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The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

COK-H01267-23-P024119 23

A-V Nodal Reentrant Tachycardia

Two Dimensional Echocardiography in Infective Endocarditis

Quantitative Coronary Arteriography

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Highly effective for many from two

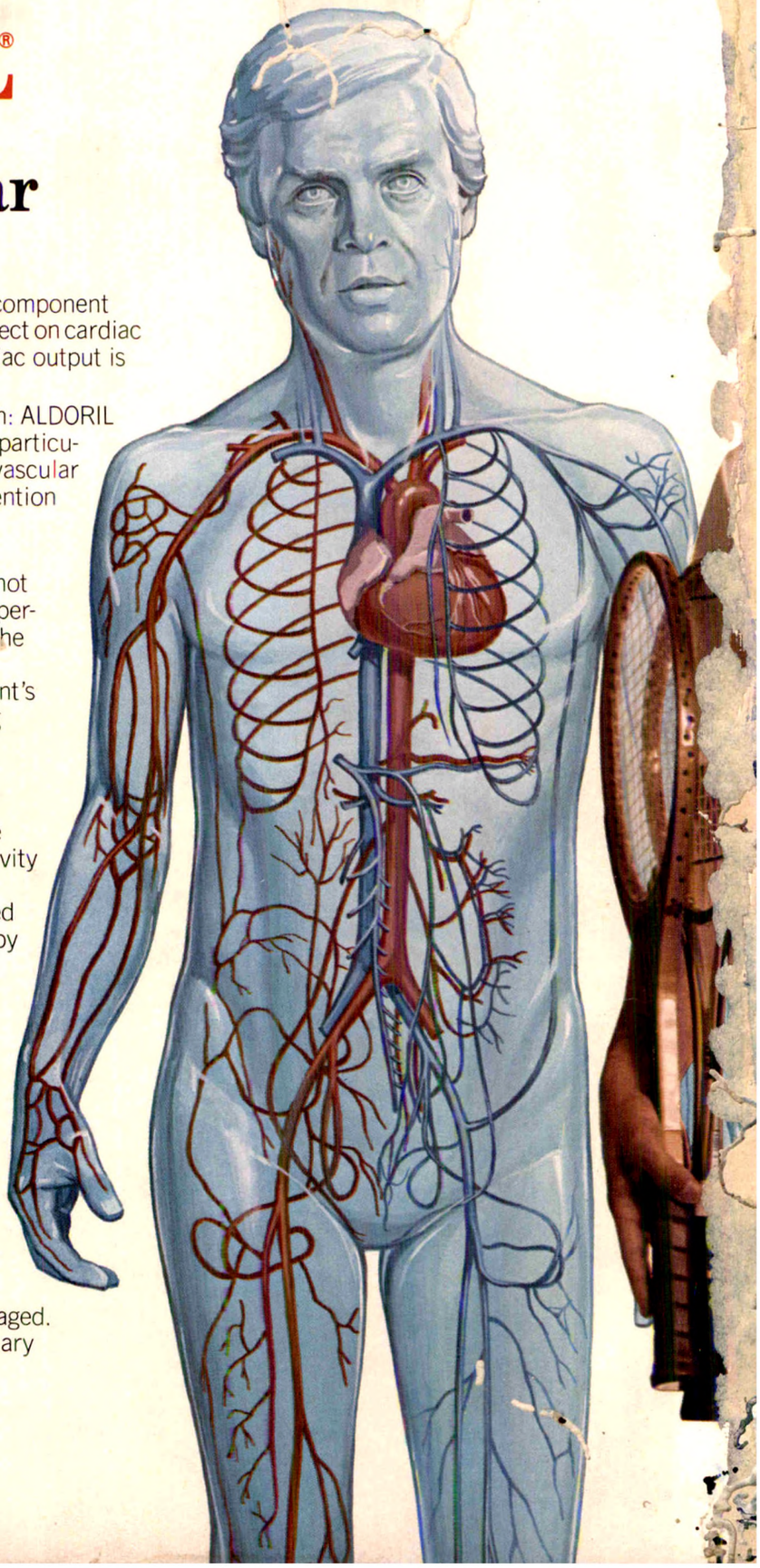
ALDORIL®
from the cardiovascular viewpoint

- ☐ A favorable cardiac profile: neither component of ALDORIL usually has any direct effect on cardiac function—in long-term therapy cardiac output is usually maintained.
- ☐ Control of sodium and fluid retention: ALDORIL often helps control fluid imbalance, particularly in those cases of hypertensive vascular disease where sodium and water retention is a problem.

As a fixed combination, ALDORIL is not indicated for initial therapy since hypertension requires therapy titrated to the individual patient. If an available strength of ALDORIL meets the patient's titrated needs, the combination drug may be more convenient in patient management. Therapy should be reevaluated as necessary.

ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.



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active hypertensives points of view



ALDORIL®
from the practical viewpoint

- ☐ Highly effective complementary agents: HydroDIURIL® (Hydrochlorothiazide, MSD), and ALDOMET® (Methyldopa, MSD), two well-accepted antihypertensives which usually maintain blood pressure control throughout the day.
- ☐ Greater dosage convenience (with a single tablet): a b.i.d. regimen is possible for many patients.
- ☐ Effect on daily activities usually minimal: there is less frequent symptomatic postural hypotension with ALDORIL than with many other antihypertensive agents. Exercise hypotension and diurnal blood pressure variations rarely occur.

ALDORIL®

containing methyldopa and hydrochlorothiazide

TABLETS
ALDORIL® D50
containing 500 mg ALDOMET® (Methyldopa, MSD) and 50 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
ALDORIL® D30
containing 500 mg ALDOMET® (Methyldopa, MSD) and 30 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
ALDORIL®-25 containing 250 mg ALDOMET® (Methyldopa, MSD) and 25 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
ALDORIL®-15 containing 250 mg ALDOMET® (Methyldopa, MSD) and 15 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

For a brief summary of prescribing information, please see following page.

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Antihypertensive TABLETS
ALDORIL® D50
methyldopa 500 mg and hydrochlorothiazide 50 mg

Antihypertensive TABLETS
ALDORIL® D30
methyldopa 500 mg and hydrochlorothiazide 30 mg

Antihypertensive TABLETS
ALDORIL®-25
methyldopa 250 mg and hydrochlorothiazide 25 mg

Antihypertensive TABLETS
ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without mild edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and bilirubin by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—***Central nervous system:*** Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. ***Cardiovascular:*** Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) ***Gastrointestinal:*** Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. ***Hepatic:*** Abnormal liver function tests, jaundice, liver disorders. ***Hematologic:*** Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. ***Allergic:*** Drug-related fever, lupus-like syndrome, myocarditis. ***Other:*** Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—***Gastrointestinal system:*** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis ***Central nervous system:*** Dizziness, vertigo, paresthesias, headache, xanthopsia. ***Hematologic:*** Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. ***Cardiovascular:*** Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). ***Hypersensitivity:*** Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. ***Other:*** Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL® D30, containing 500 mg methyldopa and 30 mg hydrochlorothiazide, bottles of 100; Tablets ALDORIL® D50, containing 500 mg methyldopa and 50 mg hydrochlorothiazide, bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486. J8AR09(023)

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The unround Offset and Offset Dx ECG monitoring electrode... specially created to solve problems.

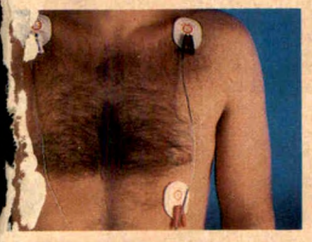
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e unique elliptical design Offset electrodes permits acement on almost any body nd ensures conformation ody contours. The special activated adhesive resists tact loss due to perspiration when used on diaphoretic ients) and loosening action sed by prep solutions.

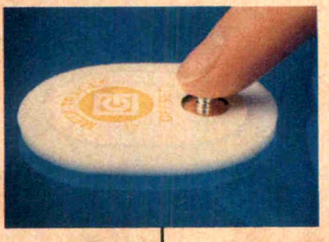
Unround to reduce motion artifact and re base-line tability.
The Medi-T set electrode separa p from the gel colur cting them with a r chloride conductor. T wa? Little or no movemen gel column, producing a superior trace that virtually eliminates motion artifact. Since the snap is over the adhesive, leadwire induced artifact and loose electrodes caused by leadwire tugging are virtually eliminated.

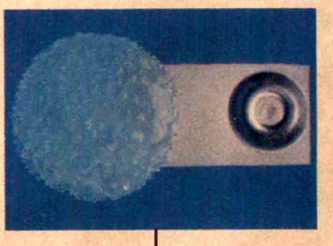
Unround, the result of new technology in ECG monitoring electrodes.*
Advanced technology assures unprecedented conductivity and an end to trace deterioration problems. Specially formulated gel prevents premature dry-out and provides low impedance for a strong, reliable trace. In actual defibrillation tests, Offset electrode trace recovery occurred in less than one second!

Uninterrupted ECG monitoring is virtually assured.

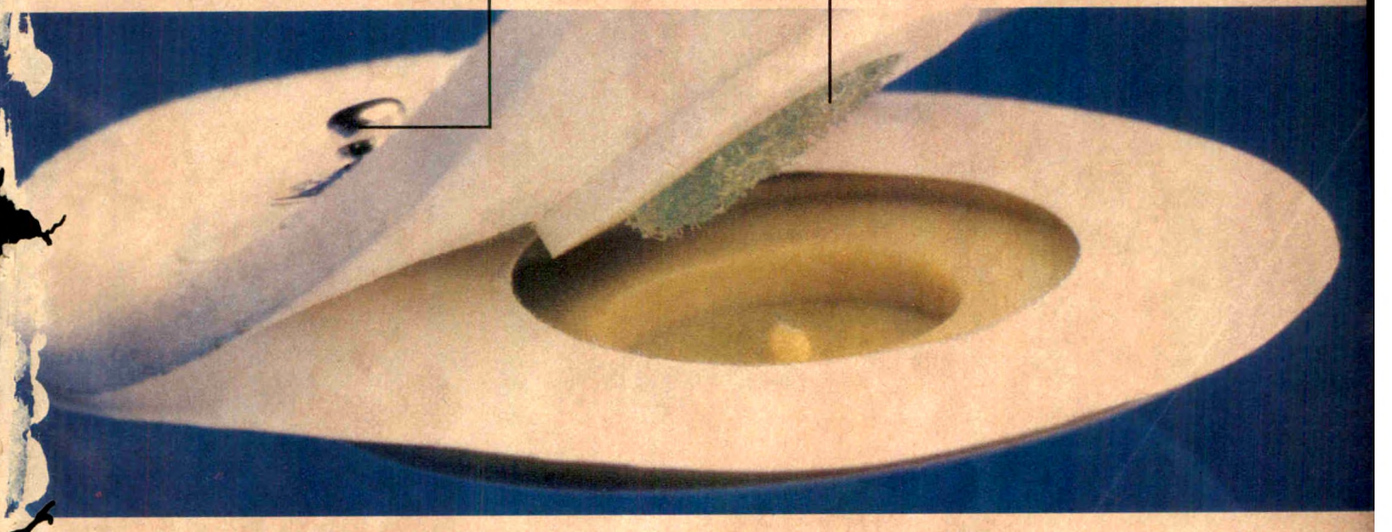
Unround to result in a superior trace.
The soft, flexible gel ring maintains a stable gel column, even during patient and/or leadwire movement. Motion artifact is greatly reduced. Further, the specially formulated low impedance gel ensures base-line stability and minimizes patient skin irritations. The result? A rapid, strong, clear trace that's trouble free.











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Unround Offset and Offset Dx... part of a total ECG monitoring system.
Packaged for your convenience, Offset electrodes are available in singles, 3's and 25's. Offset Dx electrodes come in singles, 5's and 25's. A multiple layer foil package maintains a clean product that is virtually impervious to moisture/vapor transmission.

Offset and Offset Dx are part of our total ECG monitoring system that includes a complete line of cables, leadwires, recording charts and patient record forms.

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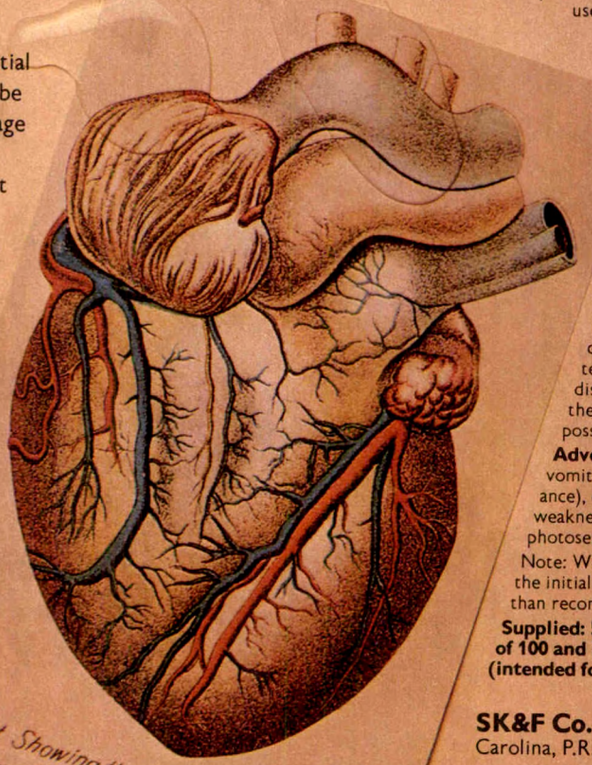
A LOGICAL ADJUNCT TO FUROSEMIDE IN CARDIAC EDEMA

In a study of 30 cardiac patients (10 as controls, 20 receiving furosemide), 'Dyrenium' (200 mg./day) was added to 10 of the treated patients. After at least 10 days on the combined regimen, mean plasma potassium was significantly increased from pre-'Dyrenium' levels of 3.85 mEq./l. (±.12) to 4.54 mEq./l. (±.12). Any K+ supplements were discontinued.[1]

'Dyrenium' Has an Additive Effect.

When used with another diuretic, initial dosage of both agents should usually be reduced; careful supervision and dosage adjustment are required. K+ supplements should be discontinued and not reinstituted unless hypokalemia develops or dietary K+ intake is markedly reduced. K+ supplements are contraindicated when 'Dyrenium' is used alone. Hyperkalemia can occur, but it is rare when renal function is normal. Serum K+ and BUN should be checked regularly (see Warnings below).

1. Donaldson, E.K., et al.: *Brit. M.J.* 1:1254-5 (May 22) 1976.



The Heart Showing the Great Arteris

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing.

'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Triamterene is a weak folic acid antagonist. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 50 and 100 mg. capsules, in bottles of 100 and in Single Unit Packages of 100 (intended for institutional use only).

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Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

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For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

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For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

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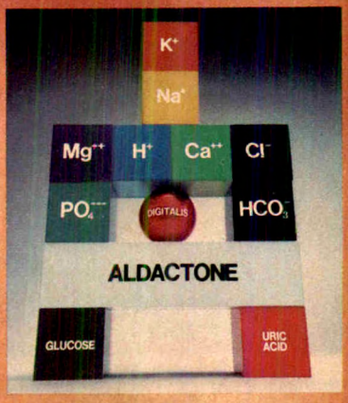
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Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Thus Aldactone should be prescribed only when other measures are considered inadequate or inappropriate. (See boxed warning and *Warnings* section of Aldactone prescribing information, a brief summary of which appears on the facing page.)



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CLINICAL STUDIES

687 **Electrophysiologic Evidence for Selective Retrograde Utilization of a Specialized Conducting System in Atrioventricular Nodal Reentrant Tachycardia**

JOSEPH ANTHONY C. GOMES, MALKIAT S. DHATT, DAVID S. RUBENSON and ANTHONY N. DAMATO

Electrophysiologic data obtained using His bundle electrograms, incremental atrial and ventricular pacing and atrial and ventricular extrastimulus techniques before and after the administration of 0.01 mg/kg of intravenous ouabain in 12 patients indicate that the site of reentry during paroxysmal supraventricular tachycardia was the region of the atrioventricular (A–V) node. Observations on the H-Ae intervals and retrograde A–V nodal conduction patterns permitted the classification of these patients into two groups. Control studies in five patients without tachycardia and studies after the administration of ouabain in group I suggest that anterograde limb of the reentry circuit was the A–V node but that the retrograde limb constituted a pathway with electrophysiologic characteristics unlike that of the A–V node. In group II both the anterograde and retrograde limbs of the reentry circuit had electrophysiologic characteristics of the A–V node. Depending on the electrophysiologic properties of the anterograde and retrograde pathways, the inherent rate of tachycardia and the response to drugs will vary.

699 **Quantitative Coronary Arteriography: Coronary Anatomy of Patients With Unstable Angina Pectoris Reexamined 1 Year After Optimal Medical Therapy**

WOLF RAFFLENBEUL, LLOYD R. SMITH, WILLIAM J. ROGERS, JOHN A. MANTLE, CHARLES E. RACKLEY and RICHARD D. RUSSELL, Jr.

In 25 patients with unstable angina pectoris coronary angiographic findings showed no significant change after 1 year of medical treatment. This rate of disease progression was substantially lower than previously reported in patients with stable angina pectoris. Only 14 of 69 stenoses (20 percent) demonstrated a marked increase in the degree of obstruction. These and other data in this study support the theory that unstable angina pectoris may be the clinical manifestation of a temporary period during the course of coronary artery disease in which a dynamic imbalance exists between myocardial blood supply and demand that leads to the profound clinical instability.

708 **Exercise-Induced Increase in Diastolic Pressure: Indicator of Severe Coronary Artery Disease**

DAVID S. SHEPS, JACK C. ERNST, FRANKLIN W. BRIESE and ROBERT J. MYERBURG

Using an increase in diastolic blood pressure of more than 15 mm Hg on at least two determinations after a treadmill exercise test in 281 symptomatic patients, these investigators found that such an abnormal response may be a good indicator of coronary artery disease even in the absence of S-T segment changes. Two hundred nine patients had a normal and 72 patients an abnormal diastolic pressure response. In a subgroup of 41 patients who underwent coronary arteriography, 50 percent of patients with a normal diastolic pressure response had normal coronary arteries compared with 17 percent of those with an abnormal response. The mechanism for this increase in diastolic blood pressure response to exercise remains to be clarified.

713 **Abnormal Electrocardiographic Responses to Exercise in Patients Referred for Noninvasive Evaluation of Occlusive Peripheral Arterial Disease**

AGENOR SILVESTRE, ARTUR DeSA'NETO, JOHN M. JOHNSON, KENNETH B. DESSER and ALBERTO BELCHIMOL

On the basis of the abnormal electrocardiographic responses to exercise in 13 of 50 consecutive patients (26 percent) noted in this study, these investigators emphasize the need for such cardiac testing in patients with sus-

Continued on page A13

*INDICATIONS—Based on a review of this drug by the National Academy of Science–National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy. Tablets of 25 mg

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pected peripheral vascular disease. Electrocardiographic monitoring during exercise in the peripheral vascular laboratory can provide useful cardiac data and improved patient safety. At present only 29 percent of the 34 peripheral vascular laboratories that responded to a questionnaire routinely perform such monitoring during exercise testing.

717 **Spectrum of Exercise Thallium-201 Myocardial Perfusion Imaging in Patients With Chest Pain and Normal Coronary Angiograms**

JOSE MELLER, STANLEY J. GOLDSMITH, ARTHUR RUDIN, AUGUSTO D. PICHARD, RICHARD GORLIN, LOUIS E. TEICHHOLZ and MICHAEL V. HERMAN

No combination of the noninvasive tests used in this study, including the exercise electrocardiographic treadmill test, clinical history and resting and exercise myocardial perfusion imaging, predicted more accurately the absence of obstructive coronary artery disease in 27 patients with chest pain than resting or exercise myocardial perfusion imaging alone. The incidence rate of false positive diagnosis was highest with the use of the clinical history of angina pectoris (55 percent), less with exercise treadmill tests (37 percent) and least with the exercise myocardial perfusion imaging test (15 percent). The last procedure also disclosed no evidence of abnormal myocardial blood flow distribution in 23 of 27 patients (85 percent) with chest pain and normal coronary arteries. The cause of abnormal myocardial perfusion imaging in the other four patients is unclear. Although these studies indicate that the exercise thallium-201 myocardial perfusion imaging test is a good noninvasive detector of normal coronary arteries in patients with chest pain, the investigators caution that a normal test does not automatically predict the absence of coronary artery disease.

724 **Reproducibility of Exercise-Induced Ventricular Arrhythmia After Myocardial Infarction**

MAGDI SAMI, HELENA KRAEMER and ROBERT F. DeBUSK

In this study of the reproducibility of exercise-induced ventricular arrhythmias the mean prevalence rate of ventricular arrhythmias among 155 men 3 to 52 weeks after myocardial infarction was 52 percent. Except for the 3 to 11 week test pairs the prevalence of premature ventricular complexes did not change significantly in the 1 year after infarction. Use of the kappa coefficient permits evaluation of the entire population. The reproducibility of categorical responses is best estimated by the kappa coefficient, which considers bidirectional variations in test results and expresses reproducibility above the chance level. The data suggest that continuous measures may be more sensitive than categorical ones and may therefore be a better choice for the clinical evaluation of ventricular ectopy.

731 **Prevalence of Diagnostic Abnormalities in Patients With Genetically Transmitted Asymmetric Septal Hypertrophy**

FOLKERT J. ten CATE, PAUL G. HUGENHOLTZ, WIM G. van DORP and JOSE ROELANDT

Echocardiographic studies in 100 patients from a general population with cardiac disease disclosed an 8 percent prevalence rate of asymmetric septal hypertrophy (defined as a ventricular septal/free posterior wall thickness ratio greater than 1.3). Additional studies in 33 patients with classic hypertrophic obstructive cardiomyopathy, in 116 of their first degree relatives and in 35 normal persons showed that this abnormal ratio alone was not a manifestation of genetically transmitted asymmetric septal hypertrophy. Echocardiographically assessed asymmetric septal hypertrophy can be considered the anatomic marker for hypertrophic cardiomyopathy only when, in addition to an abnormal ratio greater than 1.3, a decreased systolic septal thickening and an abnormal left ventricular shape are present. A practical way to exclude genetically transmitted asymmetric septal hypertrophy as a cause of such an abnormal ratio is to examine first degree relatives for asymmetric septal hypertrophy and for decreased septal thickening by echocardiography.

738 **Comparison of Two-Dimensional and M-Mode Echocardiography in the Evaluation of Patients With Infective Endocarditis**

GARY S. MINTZ, MORRIS N. KOTLER, BERNARD L. SEGAL and WAYNE R. PARRY

In this small series of 21 patients with clinically diagnosed infective endocarditis, the senstivity of two-dimensional echocardiography was similar to that of M-mode echocardiography in detecting valve vegetations. Vegetations were detected in 10 of 22 involved valves with M-mode echocardiography and in 9 valves with two-dimensional echocardiography. Two-dimensional echocardiography was superior in detecting complications of endocarditis, in its ability to visualize areas of the cardiac valves that are "silent" with the M-mode technique and in delineating the spatial relations among cardiac structures that permit the diagnosis of valve destruction. When

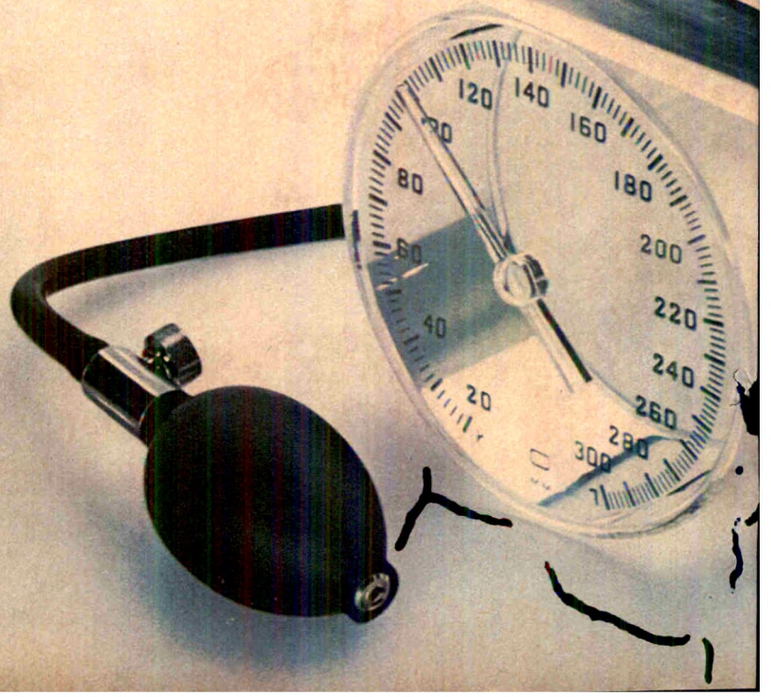
Continued on page A17

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BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria; hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored), 50 mg. (aqua) and 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips). Also, 100 mg. and 50 mg. in PAKs of 28 tablets, boxes of 6.

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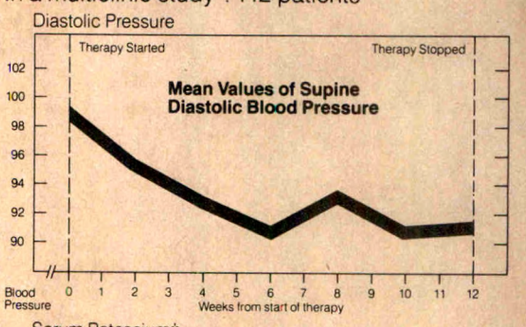
Well-documented Benefits

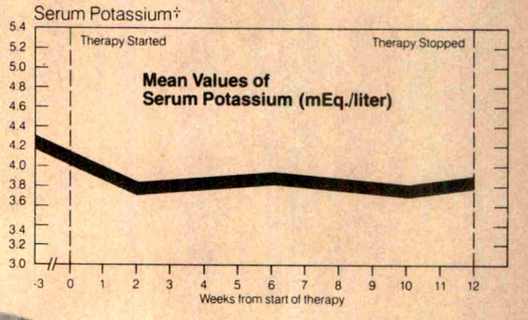
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*Multiclinic study involved 112 patients in: New Orleans, LA; Denver, CO; Nassau, Bahamas; Madison, WI; Paterson, NJ; East Meadow, NY. Data on file, USV Laboratories Inc.

†With thiazide and thiazide-like diuretics, it is possible to develop certain electrolyte imbalances including hypokalemia, hyperuricemia and hyperglycemia.

In a multiclinic study*: 112 patients

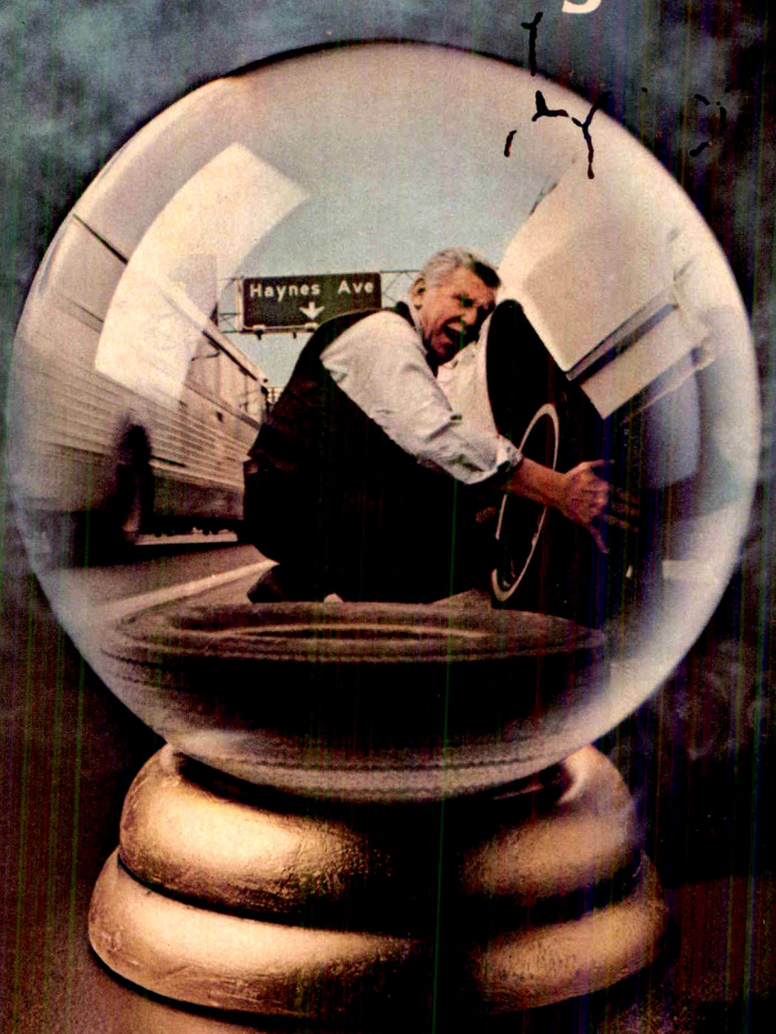






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SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

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the two techniques are combined, a vegetation or valve destruction can be detected in 80 percent of cases compared with the M-mode technique alone.

745 Inotropic Effect of Post-Stimulation Potentiation in Man: An Echocardiographic Study

JOSEPH ANTHONY C. GOMES, CLARITA R. CARAMBAS, LAURENCE M. MATHEWS, HARRIETTE E. MORAN and ANTHONY N. DAMATO

Echocardiographic studies performed in 11 human subjects during incremental atrial or ventricular pacing showed that the positive inotropic effects of such stimulation on the left ventricle are reflected as post-stimulation potentiation that is related to the pacing rate. At any given rate decay in potentiation occurred rapidly within four to five beats after pacing was stopped. For the first post-stimulation beat at maximal paced rates (146 ± 3 beats/min), the ejection fraction (+23 percent) and percent fractional shortening (+45 percent) increased significantly and volume (−52 percent) decreased significantly. Similar significant changes of a lesser magnitude occurred at lower paced rates. These observations suggest that the enhanced potentiation of the post-stimulation beat is due to an enhanced inotropic state of the left ventricle and is partly related to decreases in left ventricular afterload.

753 Role of Blood Viscosity in the Production of Innocent Ejection Murmurs

HANI N. SABBAH, TENNYSON G. LEE and PAUL D. STEIN

Studying the role of viscosity and the density of blood in producing innocent ejection murmurs, these investigators found that women with an innocent murmur had a significantly lower level of hematocrit and blood viscosity than subjects without a murmur. The increased turbulence caused by the decreased viscosity may cause inaudible ejection murmurs to exceed the threshold of audibility.

757 Platelet Function Studies in Coronary Artery Disease. V. Evidence for Enhanced Platelet Microthrombus Formation Activity in Acute Myocardial Infarction

PAULETTE MEHTA and JAWAHAR MEHTA

Using the technique for measuring in vivo platelet aggregate formation activity, these investigators found that acute transmural myocardial infarction was associated with a significant increase in circulatory platelet microthrombi. By the 7th hospital day this level gradually declines to normal in patients with an uncomplicated course. A persistently high activity or a further increase in circulating platelet microthrombi suggests continued myocardial damage. Circulating platelet microthrombi were similar in acute and convalescent phases of patients with chest pain but without myocardial infarction and were comparable with values in healthy volunteers. These data suggest that increased circulatory platelet microthrombi may be related to tissue necrosis associated with transmural myocardial infarction.

EXPERIMENTAL STUDIES

761 A Biologic Model of Parasystole

JOSE JALIFE and GORDON K. MOE

Simulating the electrotonic interactions of a parasystolic pacemaker with ventricular responses to the normal pacemaker across an area of depressed excitablility in a model consisting of strands of canine Purkinje fibers mounted in a sucrose gap preparation, these investigators confirmed the predictions of a previously described mathematical model that these patterns depend on the magnitude of the electronic influence of the evoked response on the ectopic pacemaker cycle length and on the ratio of the intrinsic frequencies. As in the mathematical model, an "ectopic" pacemaker could be entrained within wide ranges both above and below its intrinsic frequency. A constant cycle length of a protected ectopic pacemaker, evident by interectopic intervals that are simple multiples of a common denominator, is not a requirement for the diagnosis of parasystole. The studies may help distinguish between reentry and parasystole in clinical arrhythmias.

773 Mechanism of Reduction of Mitral Regurgitation With Vasodilator Therapy

CHAIM YORAN, EDWARD L. YELLING, RONALD M. BECKER, SHLOMO GABBAY, ROBERT W. M. FRATER and EDMUND H. SONNENBLICK

These open chest dog studies, designed to define the basis of the beneficial hemodynamic effects of nitroprusside in experimentally produced acute mitral regurgitation, demonstrate that the regurgitant mitral orifice is not a fixed structure and that nitroprusside reduces regurgitation by decreasing the regurgitant orifice size as a result

Continued on page A19

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of reduction in ventricular volume rather than reduction of impedance to left ventricular ejection. During the infusion of nitroprusside there was a decrease in the regurgitant volume (−26 percent), the regurgitant fraction of the total left ventricular stroke volume (−17 percent) and the calculated area of the mitral regurgitant orifice area (−18 percent). The administration of nitroprusside also reduced both peak systolic and left atrial pressures.

METHODS

778 Detection of Coronary Artery Disease With Rapid Serial Rescanning With Potassium-43 at Rest

ANGEL K. MARKOV, ROBERT O. SMITH, PATRICK H. LEHAN, JAMES R. GALYEAN, III, GASTON RODRIGUEZ and HARPER K. HELLEMS

This rapid serial rescanning technique with potassium-43 at rest detected coronary arterial lesions of 50 percent or greater, collateral circulation and, often, ventricular aneurysms as positive images. For 32 patients who underwent myocardial imaging at rest and after graded exercise testing, the images at rest correlated better with the angiographic data. For a clinical setting this rapid serial rescanning technique may prove more valuable than the present static imaging techniques. In the majority of cases it will eliminate the need for post-exercise imaging and provide data for detecting an impaired regional myocardial metabolic state when the disease is inaccessible to coronary angiography.

787 Thallium-201 Myocardial Perfusion Scintigraphy: Results of Standard and Multi-Pinhole Tomographic Techniques

ROBERT A. VOGEL, DENNIS L. KIRCH, MICHAEL T. LeFREE, JOSEPH O. RAINWATER, DOUGLAS P. JENSEN and PETER P. STEELE

A new method of cardiac tomography using a seven pinhole collimator, a standard 37.5 cm diameter crystal Anger camera and a digital computer proved highly sensitive to and specific for the presence of coronary artery disease using stress thallium-201 imaging. The ability to obtain seven views within 10 minutes may add to the improved detection of coronary artery disease with this technique. Another advantage is that this technique can be rapidly performed with generally available nuclear medicine resources.

794 Photokymography: A Noninvasive Method of Detecting Ischemic Segmental Myocardial Wall Motion Abnormalities

MAX PICHLER, GEORGE A. DIAMOND, MICHAEL HIRSCH, RAN VAS, DAN TZIVONI, H. J. C. SWAN and JAMES S. FORRESTER

As assessed in these studies of seven closed chest dogs undergoing acute balloon occlusion of the left circumflex coronary artery, photokymography is a new, simple and sensitive noninvasive technique for detecting acute ischemic segmental wall motion abnormalities. It provides a relatively low cost beat to beat recording that can be evaluated with several increments in stress and can be more accurately analyzed than is possible with use of visual inspection of the real time image alone, especially at higher heart rates. Despite a few drawbacks discussed by the investigators, photokymography appears to be a promising method for the clinical evaluation of suspected ischemic heart disease in man.

REPORTS ON THERAPY

801 Prospective Randomized Trial of Glucose-Insulin-Potassium in Acute Myocardial Infarction

WILLIAM J. ROGERS, PETER H. SEGALL, HUEY G. McDANIEL, JOHN A. MANTLE, RICHARD O. RUSSELL, Jr. and CHARLES E. RACKLEY

Although the number of patients (50) in this ongoing randomized controlled clinical trial of the value of intravenous glucose-insulin-potassium infusion in the management of acute myocardial infarction is too small to permit definite conclusions, the data demonstrate that the infusion (1) does not adversely alter hemodynamics (2) reduces free fatty acids, (3) diminishes the frequency of ventricular arrhythmias and (4) has no demonstrable effect on infarct size as assessed with creatine kinase isoenzyme values. The hospital mortality rate was 15 percent (4 of 27) in the conventionally treated control group and 13 percent (3 of 23) in the group treated with glucose-insulin-potassium infusion.

Continued on page A21

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CONTENTS

810 Paradox of Improved Exercise but Not Resting Hemodynamics With Short-Term Prazosin in Chronic Heart Failure

STANLEY A. RUBIN, KANU CHATTERJEE, HARRIS J. GELBERG, THOMAS A. PORTS, BRUCE H. BRUNDAGE and WILLIAM W. PARMLEY

Short-term, oral prazosin administered to 10 patients with severe chronic failure significantly increased cardiac output and stroke volume and decreased the arteriovenous oxygen difference and left ventricular filling pressure during exercise but not at rest. This drug affects hemodynamics during exercise when its pharmacologic activity as an alpha adrenergic blocking agent is most prominent. This study demonstrated that in patients with severe chronic failure the oral administration of prazosin improved left ventricular performance but did not improve the peripheral utilization of oxygen. Hemodynamic changes caused by prazosin during rest were inconsistent and did not predict changes during exercise. Prazosin may be a useful vasodilator for treating some patients with chronic heart failure, especially those whose symptoms are most severe during exercise.

PEDIATRIC CARDIOLOGY

816 Single and Two Dimensional Echocardiographic Features of the Interatrial Septum in Normal Subjects and Patients With Atrial Septal Defect

JAY N. SCHAPIRA, RANDOLPH P. MARTIN, ROBERT E. FOWLES and RICHARD L. POPP

Simultaneous M mode and two dimensional echocardiograms in 10 normal subjects and in 9 patients with a secundum atrial septal defect indicate that such studies cannot reliably differentiate a secundum atrial septal defect from a normal septum and that the medial location of the interatrial septum should be appreciated so that it will not be confused with a left atrial mass. This study also demonstrates the benefit of combining two dimensional and M mode echocardiography to improve identification of specific echoes recognized in M mode tracings. Physical limitations such as "echo dropout" are common to both the M mode and two dimensional techniques.

820 Right Atrial Ultrastructure in Congenital Heart Disease. II. Atrial Septal Defect: Effects of Volume Overload

JOHN J. FENOGLIO, Jr., TUAN DUC PHAM, ALLAN HORDOF, RICHARD N. EDIE and ANDREW L. WIT

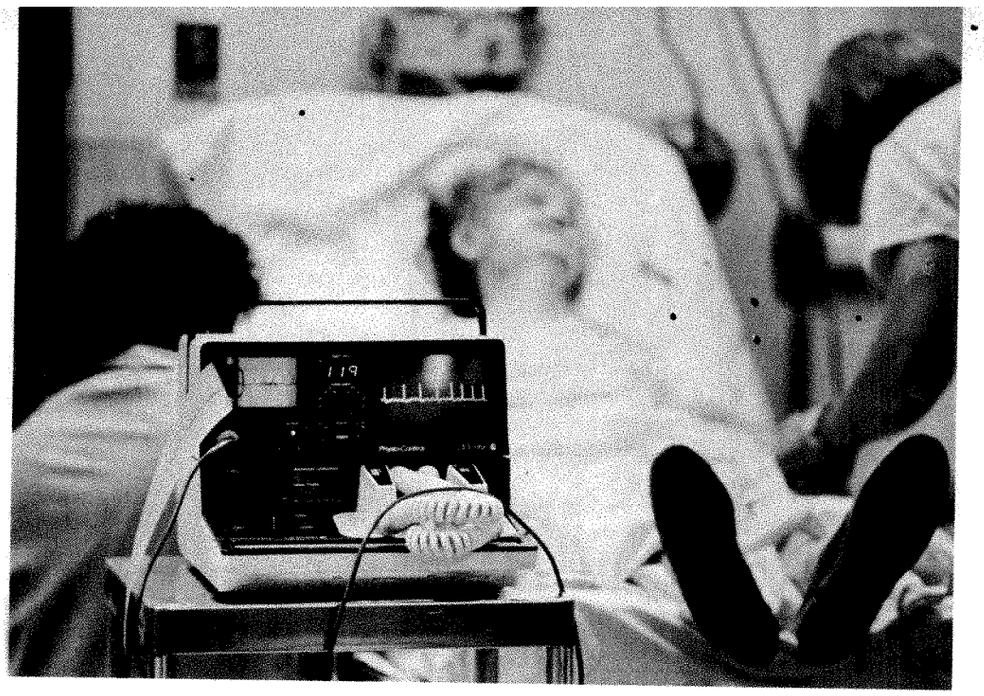
This study on portions of operatively resected right atrium from 15 patients with atrial septal defect suggests that increased right atrial blood flow without increased right atrial mean pressure is not associated with structural changes of the right atrium. In 3 of the 15 patients with elevated right atrial mean pressure and increased right atrial blood flow the atrial myocardial cells were hypertrophied; two of these had evidence of local cell degeneration. Right atrial dilation unlike left atrial dilation need not be associated with atrial arrhythmias.

828 Role of the Renin-Angiotensin-Aldosterone System in Hypertensive Children With Coarctation of the Aorta

BRUCE S. ALPERT, HUGH H. BAIN, J. WILLIAMSON BALFE, B. S. LANGFORD KIDD and PETER M. OLLEY

Clinical studies in 20 hypertensive patients with coarctation of the aorta, 8 patients with essential hypertension and 13 control subjects show similar plasma renin activity values in all during normal and low sodium diets. After the administration of furosemide, plasma renin activity levels were significantly higher in the patients with coarctation than in the other two groups. The renin and aldosterone responses and body fluid spaces in the patients with coarctation suggest that their hypertension resembles a one-kidney Goldblatt model. Although corrective surgery remains the therapy of choice, the high recurrence rate of coarctation after surgery in infancy and early childhood makes medical management desirable until the patient is old enough for operative repair. If therapy of the hypertension is necessary, a beta adrenergic blocking drug with or without a diuretic agent may be useful to decrease the cardiac index, block renin secretion and decrease extracell fluid and plasma volumes.

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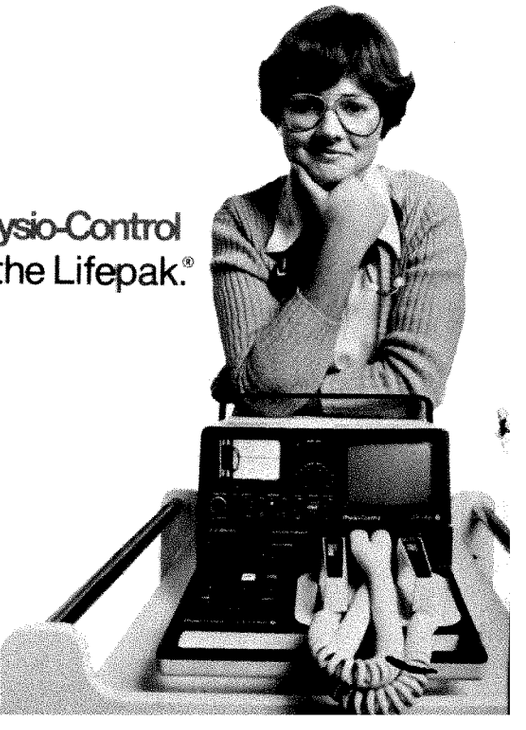
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REVIEWS

835 Coarctation of the Aorta: Review of 234 Patients and Clarification of Management Problems

RICHARD R. LIBERTHSON, D. GLENN PENNINGTON, MARSHALL L. JACOBS and WILLARD M. DAGGETT

This review of the records and follow-up clinical course of 234 patients with coarctation of the aorta clarifies still unanswered questions pertinent to the management of such persons. The data in this study suggest that the optimal time for elective surgical correction of coarctation is between the ages of 1 and 5 years. Preoperative congestive heart failure occurred in 67 percent of patients under age 1 year and over age 40 and in only 4 percent of those aged 1 to 40 years. Bacterial endocarditis, cerebral vascular accident, myocardial infarction and aortic dissection were present in 2, 6, 3 and 2 percent of patients, respectively. Their incidence increased with advancing age. Additional congenital heart lesions were present in 34 percent of the patients. Systemic hypertension was the most frequent acquired complication. Eighty percent of the 138 patients under the age of 19 years and 84 percent of the 96 patients aged 19 years and older were hypertensive.

841 Toxoplasmic Infection in Cardiac Disease

DAVID LEAK and MOHAMMED MEGHJI

Although toxoplasmic myocarditis is considered a rare disease, it is a fairly common cause of heart disease in Hamilton, Ontario where it was the etiologic factor in 18 patients who presented with heart disease in less than 2 years. Clinically these patients had cardiac arrhythmias, atypical chest pain, pericarditis and cardiac failure. Cats, uncooked meat and congenital infection were the main sources of this infection. Serial toxoplasmic antibody tests indicated that the infection was chronic in all patients except one. Experimental, serologic and epidemiologic data suggest that local myocarditis occurs most frequently during the chronic phase of toxoplasmic infection. The diagnosis requires the exclusion of other specific forms of heart disease and the establishment of evidence of toxoplasmosis with serologic testing. Patients with this form of heart disease have a potentially poor and unpredictable prognosis with serious relapse after chemotherapy.

DIAGNOSTIC SHELF

850 Echocardiographic Manifestations of Persistence of the Right Sinus Venosus Valve

JUAN BATTLE-DIAZ, PAUL STANLEY, CHRISTA KRATZ, JEAN-CLAUDE FOURON, RONALD GUERIN and ANDRÉ DAVIGNON

A newborn girl with persistence of the right sinus venosus valve showed all the clinical features of severe obstruction of the outflow tract of the right ventricle. An echocardiogram suggesting a right atrial myxoma, an unlikely finding in a neonate, is an important diagnostic clue to this anomaly. This diagnosis should be made soon after birth because surgical correction of this serious anomaly may be possible. In this case the patient did not survive operation.

854 Echocardiographic Features of Supracristal Ventricular Septal Defect With Prolapsed Aortic Valve Leaflet

KALIM U. AZIZ, ROGER B. COLE and MILTON H. PAUL

The echocardiographic M mode features of a supracristal ventricular septal defect with prolapsed right coronary aortic leaflet, as found in four children aged 2 to 10 years, include (1) the position of the ventricular septal defect as a clear space between the interrupted septal echoes below the aortic root and (2) the prolapsed right coronary aortic leaflet as anomalous linear echoes in the right ventricular outflow tract. Sector scanning using the long axis view showed the supracristal ventricular septal defect as a clear space between the top of the ventricular septum and the anterior segment of the aortic root in three of the four patients. The right coronary aortic leaflet was seen to prolapse into the right ventricular outflow tract through this defect and its motion could be clearly followed during systole and diastole. This lesion is important to diagnose early because its progressive nature causes increasingly severe aortic insufficiency, and patients with this defect have a greater susceptibility to bacterial endocarditis than those with a simple ventricular septal defect.

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CASE REPORTS

860 Propranolol in Human Plasma and Breast Milk

JOHN H. BAUER, BRIAN PAPE, JAMES ZAJICEK and TED GROSHONG

After the oral administration of a single 40 mg dose of propranolol and continuous 40 mg doses 4 times daily in a nursing mother, breast milk and plasma concentrations of propranolol peaked between 2 and 3 hours after dosing. Propranolol concentrations in breast milk were less than 40 and 64 percent, respectively, of peak plasma propranolol concentrations after single dose and continuous dose administration. The dosage ingested by this breast-feeding infant is approximately 1/100 of that used for therapeutic purposes. However, because hepatic microsomal enzyme systems responsible for metabolism are immature in newborn infants, nursing infants should be closely evaluated for bradycardia or evidence of hypoglycemia.

SPECIAL DEPARTMENTS

866 Letters to the Editor

Bypassing the Bypass With Percutaneous Transluminal Coronary Angioplasty—L. G. Bentivoglio

NHLBI Position on Percutaneous Transluminal Coronary Angioplasty (PTCA)—R. I. Levy, M. J. Jesse and M. B. Mock

Anginal Chest Pain Versus Angina Pectoris—G. M. Lawrie, G. C. Morris, Jr., W. B. Kannel and P. Sorlie

870 American College of Cardiology News

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Contents: *Natural History of Coronary Artery Disease; Precordial Movements in Coronary Artery Disease; Echocardiography in Coronary Artery Disease; Radionuclide Studies in Coronary Artery Disease; Exercise Testing and Coronary Artery Disease; Unstable Angina Pectoris—Review and Present Management; Coronary Arteriography: Indications, Contraindications and Attendant Risks; Cardiac Catheterization Evaluation of Left Ventricular Function in Stable Coronary Artery Disease; Calibration of Noninvasive Techniques; Cardiac Catheterization Evaluation of Left Ventricular Function in Stable Coronary Artery Disease—Left Ventricular Biplane Angiography; Clinical Responses to Short and Long Acting Nitrates in Coronary Artery Disease; Myocardial Metabolism in Coronary Artery Disease; Coronary Artery Bypass Grafting; Recognition of Acute Myocardial Infarction; Management of Acute Myocardial Infarction; Coronary Arteriography Within Two Months of Acute Myocardial Infarction.*

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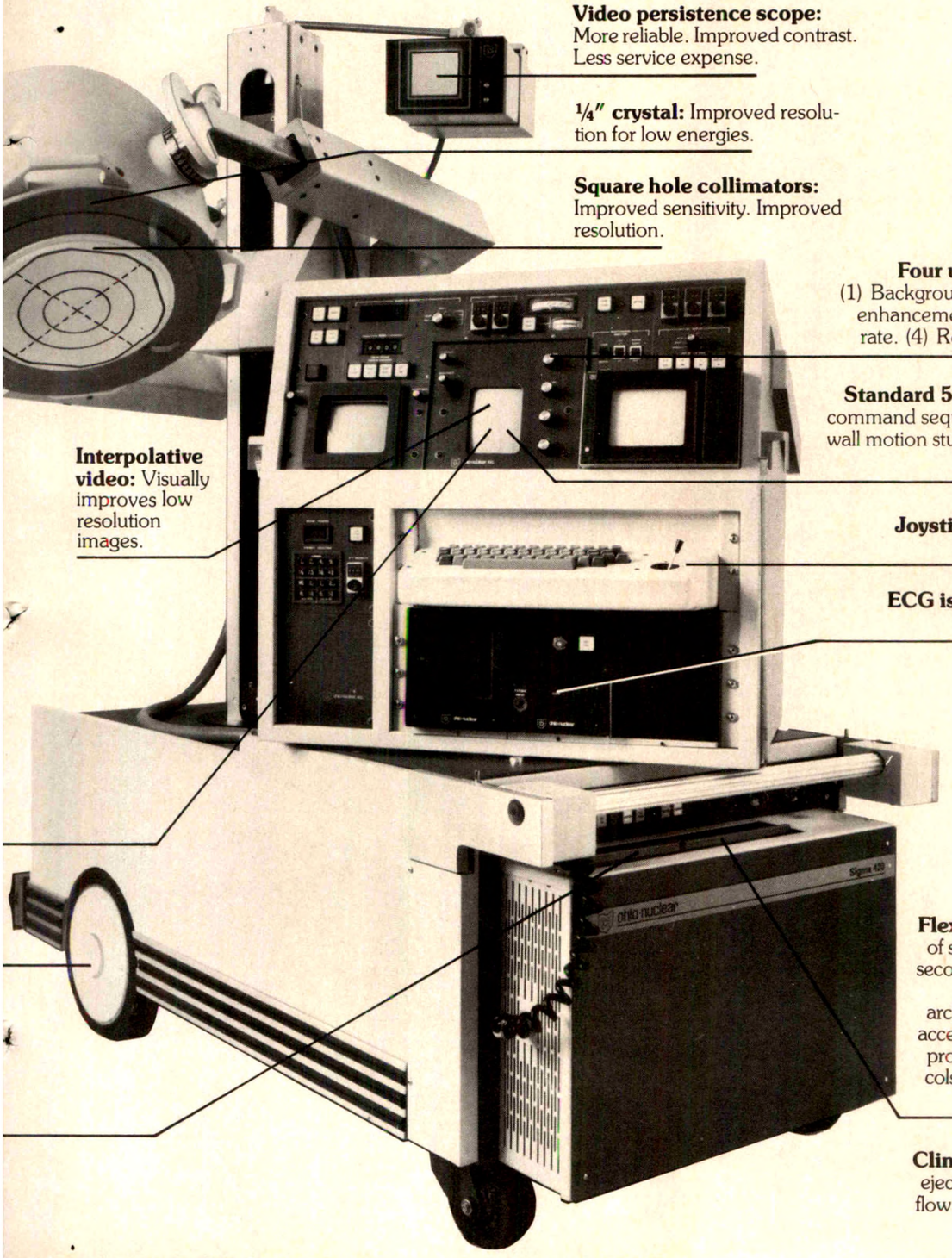
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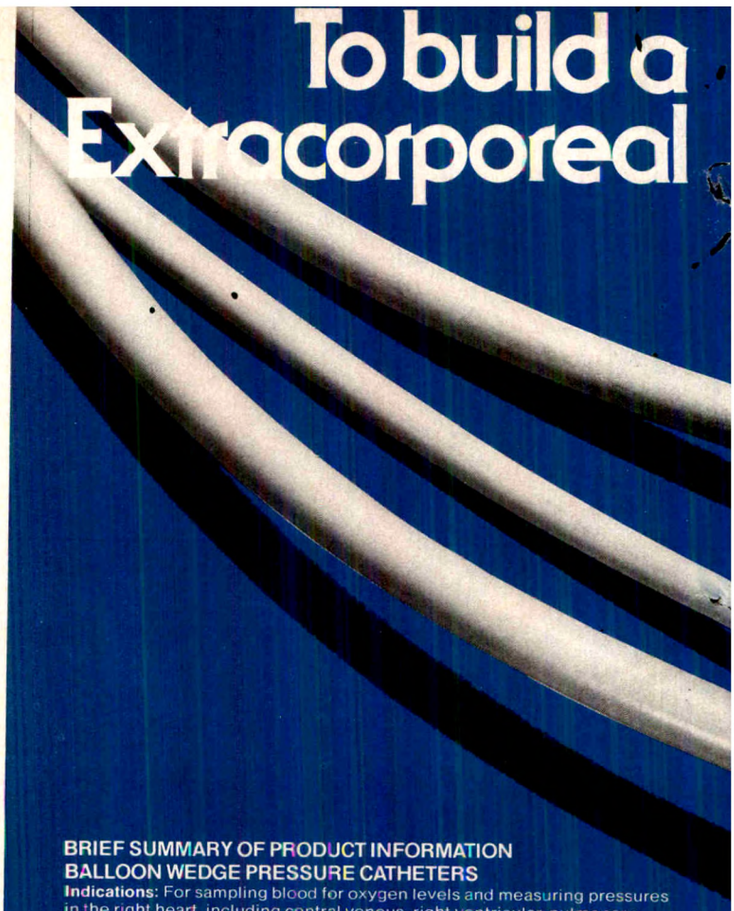
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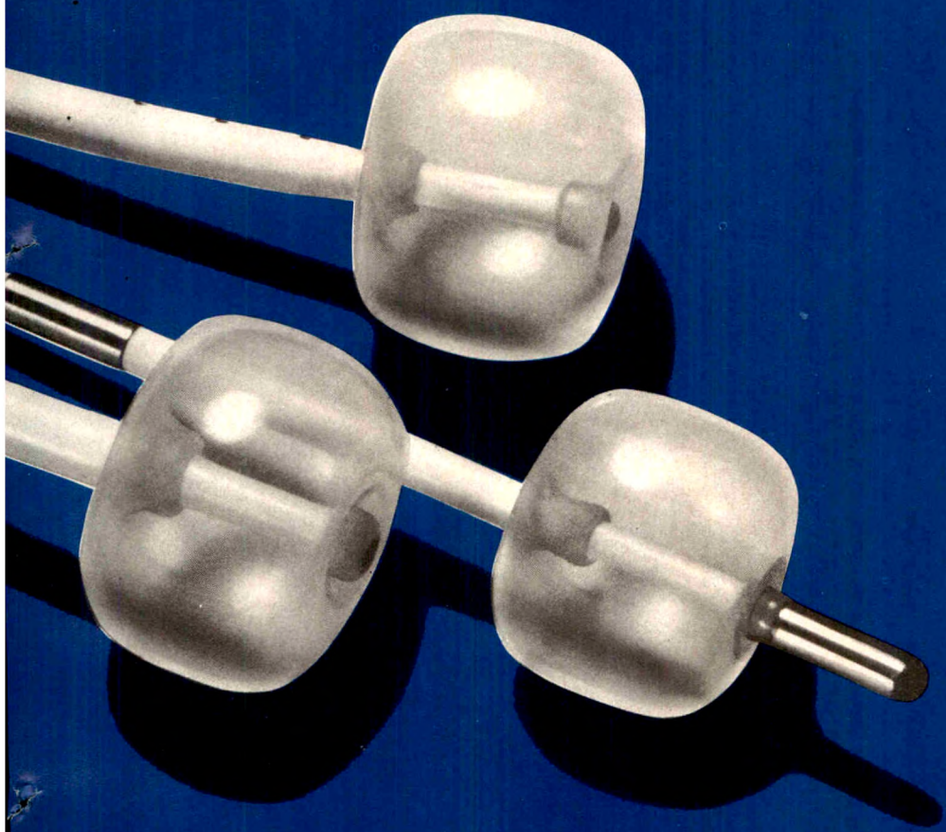
BRIEF SUMMARY OF PRODUCT INFORMATION
BALLOON WEDGE PRESSURE CATHETERS
Indications: For sampling blood for oxygen levels and measuring pressures in the right heart, including central venous, right ventricular, pulmonary artery, and pulmonary artery wedge pressure. Also indicated in anatomical cardiac defect cases to sample blood and measure pressures in any chambers that can be entered from the right heart. **Warning:** Pulmonary artery perforation, thrombosis, segmental pulmonary infarction, transient obstruction of the pulmonary outflow by the inflated balloon, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of the catheter have been reported as complications of the use of balloon catheters. Balloon rupture with possible latex embolus is a potential complication in the use of balloon catheters. **Precaution:** In pressure monitoring at bedside when catheter has been introduced in an antecubital vein, patient's arm should be immobilized to reduce the possibility of catheter advancement due to arm motion.

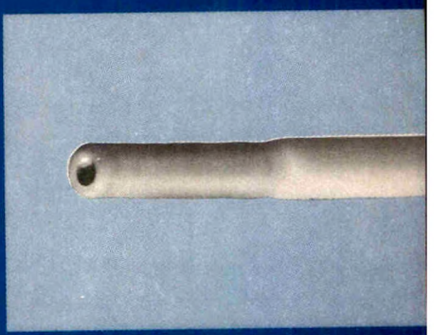
BERMAN ANGIOGRAPHIC CATHETER
Indications: For use in right-heart catheterization for cardiac angiography, pulmonary angiography, and measurement of right-heart and pulmonary artery pressures. It can be used to inject radiopaque media and measure pressures in any chambers and vessels that can be entered from the right heart. **Warnings:** Angiograms should be done with balloon inflated to minimize myocardial staining. When injecting radiopaque media, do not exceed stated maximum flow rate and pressure. Transient obstruction of the pulmonary outflow tract, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of catheters are reported complications of the use of balloon catheters. Balloon rupture with possible latex embolus is a potential complication in the use of balloon catheters. **Precaution:** Manipulate catheter carefully and gently to avoid kinking or knotting.

BIPOLAR TEMPORARY PACING W/STYLET AND BALLOON TEMPORARY PACING CATHETERS
Indications: For temporary transvenous cardiac pacing when impulse formation or conduction is impaired. **Warnings:** Myocardial perforation, fibrillation and arrhythmia, pulmonary embolism, thrombus formation, and infection are general complications of transvenous pacing. Balloon rupture with possible latex embolus, vessel perforation, and intimal disruption are potential complications of use of balloon temporary pacing catheters. With the transbrachial approach, malpositioning and perforation occur more frequently due to arm movement. Pneumothorax, air embolism, and puncture of the subclavian artery have been reported with the subclavian approach. **Precautions:** Avoid kinking or bending catheter to prevent damage to internal wires or occlusion of inflation lumen (in balloon pacing catheter). Maintain insertion site with regular meticulous redressing performed with aseptic technique. Remove stylet from Bipolar Pacing Catheter after it is in position because leaving stylet *in situ* increases the potential for perforation.

FOR BALLOON CATHETER USE, IN GENERAL
General Warnings: Carbon dioxide must be used to inflate balloon if there is a possibility that balloon rupture would result in air embolism in the left heart or systemic circulation. Do not inflate balloon beyond stated maximum inflation capacity. Exercise care when passing catheters in patients with left bundle-branch block because right bundle-branch block induced by traumatic catheter passage could result in complete heart block and asystole. **General Precautions:** Do not use liquids as balloon-inflation media. Pass catheter with continuous cardiographic monitoring and fluoroscopic guidance, and confirm final tip position by X-ray. Deflate balloon prior to withdrawing catheter to avoid possible valve damage. Use aseptic technique throughout procedure. All catheters are for single use only. Do not resterilize or reuse. Federal law (U.S.A.) restricts these devices to sale by or on the order of a physician. **Contraindication**: Not for use except as indicated.
For complete use information, see the package insert.

better cardiac catheter, starts with a built-in tip.





The Extracorporeal built-in tip, balloon deflated.



Other manufacturer's built-on tip, balloon deflated.

As you can see, the Extracorporeal tip is smooth, tapered, unruffled, suture free, no wider than the catheter itself. The benefits are built-in:

- **The introducer is the same size as the catheter.*** Not larger. This means a smaller insertion hole and less likelihood of trauma and intimal damage. And it simplifies introducer selection.
- **Less blood is lost.** Because the introducer is smaller and because the catheter fits it snugly the entire length of the catheter.
- **Our tapered tip has a larger lumen** which reduces the likelihood of clotting and makes it easier to introduce drugs and dyes.
- **A smaller diameter catheter may be used,** because a larger lumen also produces pressure measurements that can be matched only by a larger-diameter competitive catheter.
- **The tip is suture-free,** eliminating clotting caused by the sutures' irregular surface.

Beyond the tip, a host of other benefits.

- **Inflation is more convenient** because every Extracorporeal balloon catheter is packaged with an appropriately sized syringe.
- **Pure platinum electrodes for better electrical characteristics.** Blood may alter the conductivity properties of stainless steel and cause inferior readings. That's why our balloon pacing catheters employ only inert platinum for electrodes.
- **High pressure tubing** used in our Berman angiographic catheters permits higher pressures to be when drugs or dye must be injected
- **More sizes available.** Especially in Berman angiographic and wedge pressure models. And we can supply custom catheters, too.
- **Even our package works hard for you.** Each catheter comes in its own sterile peel-pack that stores easily and has a fold down tab for quick identification.
- **Our new brochure has all the facts.** Just let us know where you are and we'll send you one. Call your Extracorporeal representative, or write or call us toll free: 800-523-1740.

*With one small exception—the Extracorporeal 4F size uses a 4-1/2 size introducer.

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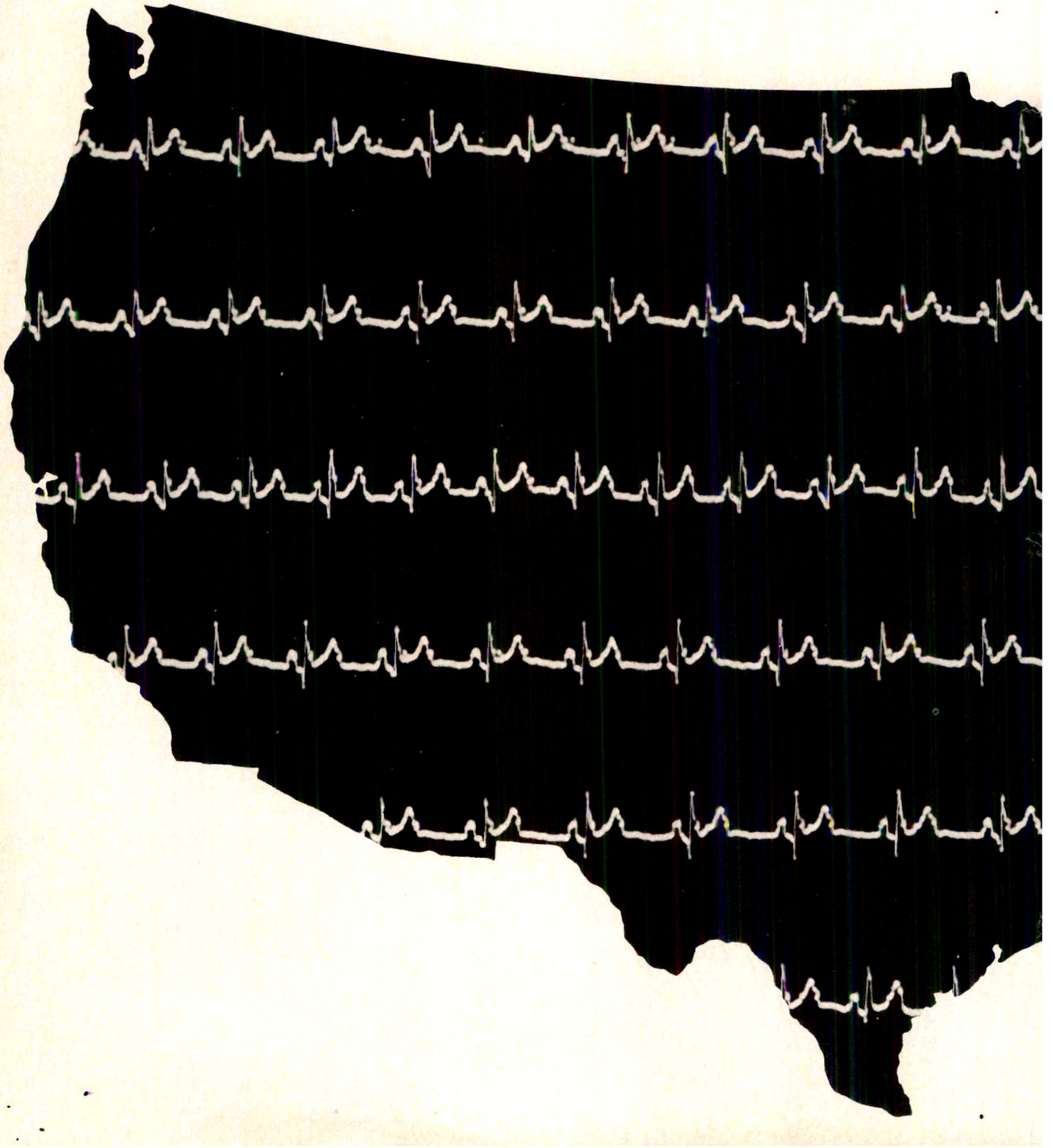
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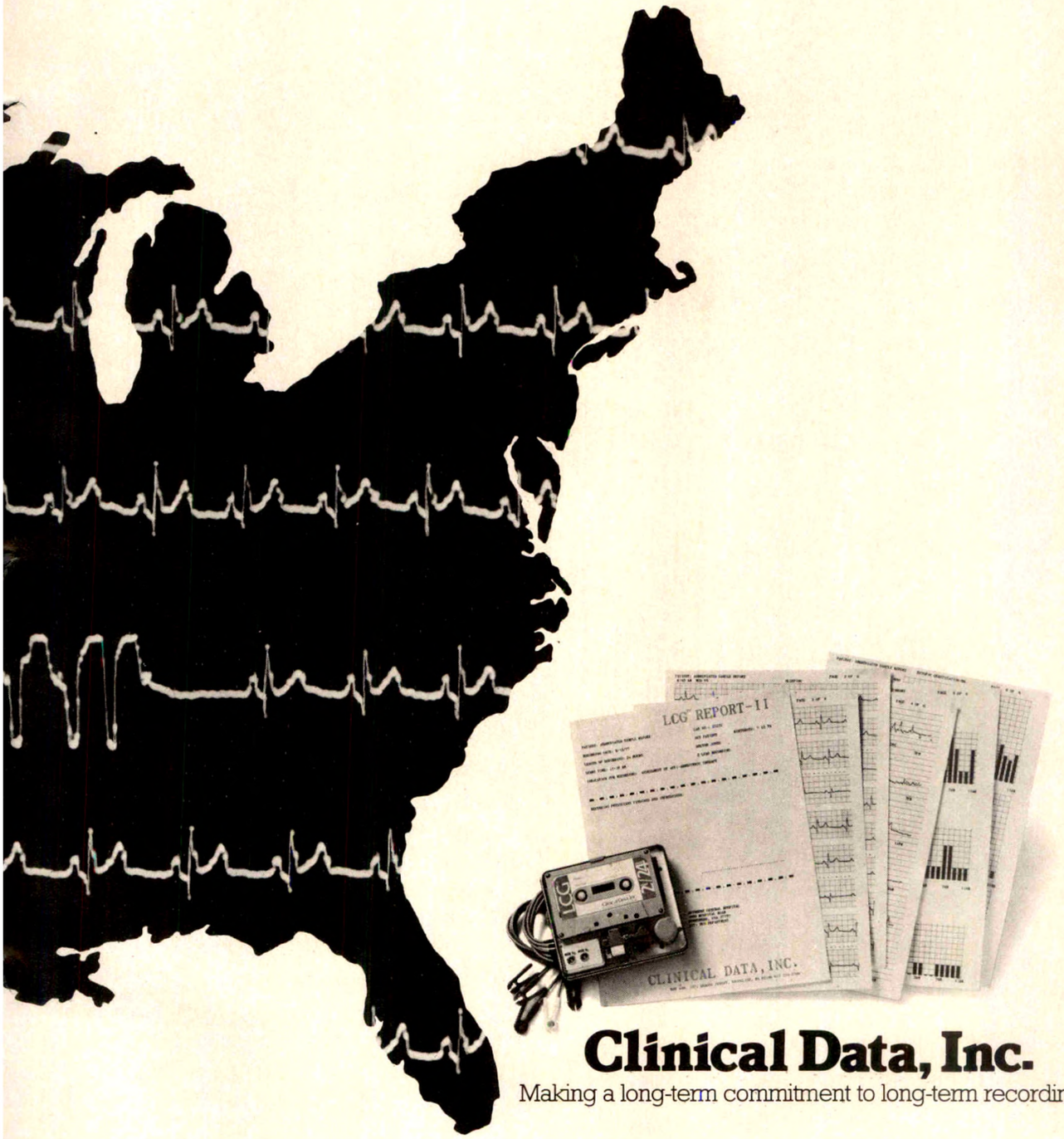


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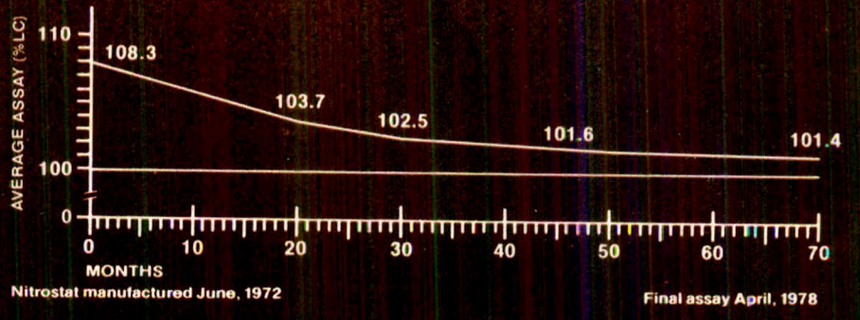
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WITHOUT COMPROMISE OF VITAL ORGANS



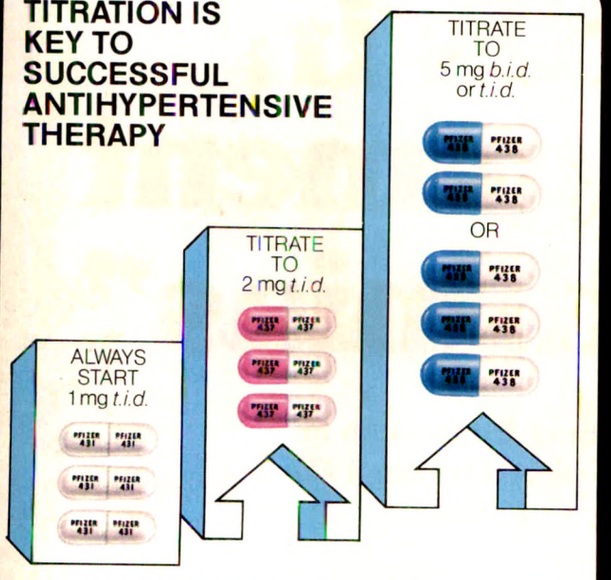
Please see Brief Summary on last page
Before prescribing Minipress, **WARNINGS** and **DOSAGE AND ADMINISTRATION** sections should be carefully reviewed.

MINIPRESS® Capsules 1mg, 2mg, 5mg
(prazosin HCl)

YEARS OF BLOOD PRESSURE CONTROL...WITHOUT COMPROMISE OF VITAL ORGANS

MINIPRESS® Capsules 1mg, 2mg, 5mg (prazosin HCl)

TITRATION IS KEY TO SUCCESSFUL ANTIHYPERTENSIVE THERAPY



USUAL MAXIMUM DAILY DOSAGE: 20 mg given in divided doses (*b.i.d.* or *t.i.d.*). A few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses.

■ **Initial therapy:** Whether using Minipress in combination with other agents or alone, the starting dosage is 1 mg *t.i.d.* If response is not adequate by the next visit, the dosage should be increased to 2 mg *t.i.d.*

■ **Dosage titration:** Thereafter, titrations of Minipress should be carried out according to patient response. Dosage may be slowly increased to a daily maximum of 20 mg given in divided doses. Although some patients may be controlled on 1 mg *t.i.d.*, generally 6 mg to 15 mg daily will be needed in the majority of responding patients in order to achieve optimal blood pressure control.

■ **Maintenance therapy:** After initial titration, patients may be maintained on a *b.i.d.* or *t.i.d.* dosage regimen.

■ If optimum control is not achieved in patients receiving Minipress and a diuretic, consider adding another Step 2 antihypertensive agent.

■ If optimum control is not achieved with Minipress as the initial agent, consider adding a diuretic.

■ When adding a diuretic or other antihypertensive agent, Minipress dosage should be reduced to 1 mg or 2 mg *t.i.d.* and retitrated as needed.

■ Available in .1-mg, 2-mg, and 5-mg capsules.

REMOVE PAGE AND FOLD ALONG DOTTED LINE AND SAVE FOR REFERENCE

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit-dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Pfizer

LABORATORIES DIVISION

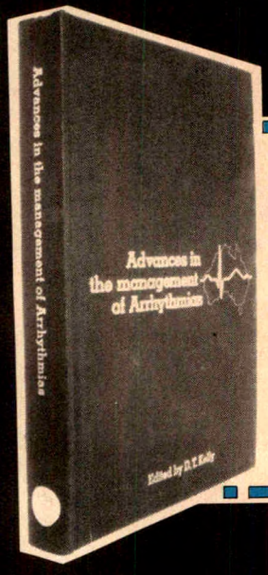
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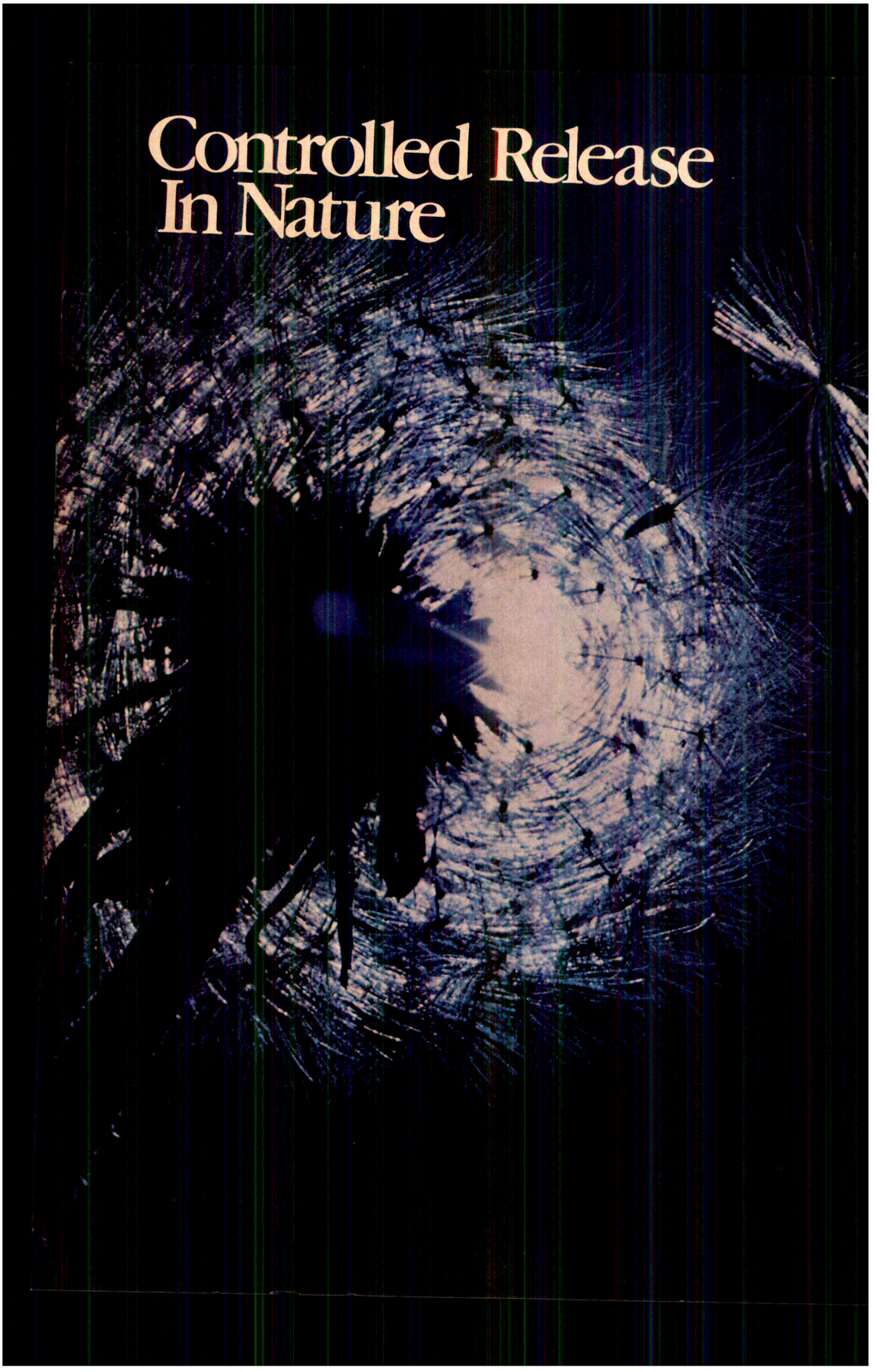
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Controlled Release In Nature



Controlled Release In Potassium Therapy

KAON-CL TABS®

(potassium chloride) Controlled Release Tablets

helps encourage adherence to prescribed dosage schedules

When patient compliance with liquids or effervescent potassium is a problem, consider the convenience of the controlled release tablet from Warren-Teed. Just 2 KAON-Cl TABS t.i.d. equal 40 mEq potassium chloride.

minimizes the possibility of high localized concentrations of potassium in the GI tract

The reported frequency of GI lesions with wax-matrix tablets is less than 1 per 100,000 patient years. There have been only two equivocal cases of GI bleeding reported with KAON-Cl TABS to date and no reports of small bowel stenosis or ulceration. However, clinical experience is insufficient at this time to indicate the incidence is other than the stated numerical ratio.

BRIEF SUMMARY
KAON-Cl TABS® (potassium chloride)
Controlled Release Tablets

Description: Kaon-Cl Tabs is a sugar coated (not enteric-coated) tablet containing 500 mg potassium chloride (equivalent to 6.7 mEq potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: *Hyperkalemia*—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-Cl Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon-Cl Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

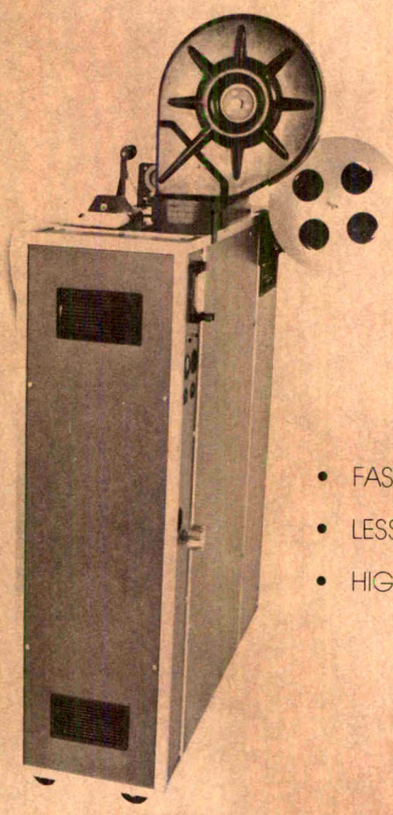
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FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.

The following infections usually respond to adequate dosage of IM penicillin G benzathine.

Streptococcal infections (Group A—without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).

Venereal infections —Syphilis, yaws, bejel, and pinta.

Medical conditions in which penicillin G benzathine therapy is indicated as prophylaxis:

Rheumatic fever and/or chorea —Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures if superinfection occurs.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

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Digoxin should be continued after heart failure is abolished unless some known precipitating factor is corrected.

2. Atrial fibrillation: Atrial fibrillation, especially when the ventricular rate is elevated. Digoxin rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

3. Atrial flutter: Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digoxin at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digoxin if failure ensues or if atrial flutter is a frequent occurrence.

4. Paroxysmal atrial tachycardia: Oral digoxin may be used, especially if the condition is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if heart failure has ensued or paroxysms recur frequently, digoxin should be maintained by oral administration.
Digoxin is not indicated in sinus tachycardia unless due to heart failure.

5. Cardiogenic shock: The drug is often employed, especially when the condition is accompanied by pulmonary edema. Digoxin seems to affect adversely shock due to septicemia from gram-negative bacteria.

CONTRAINDICATIONS: The presence of toxic effects (see ADVERSE REACTIONS section) induced by any digitalis preparation is a contraindication to all of the glycosides.
Allergy, though rare, does occur. It may not extend to all preparations, and another may be tried.
Ventricular fibrillation.

WARNINGS:

> Digitalis alone or with other drugs has been promoted for use in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

Many of the arrhythmias for which digoxin is advised closely resemble those reflecting digoxin intoxication. If the possibility of digoxin intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.
The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digoxin intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.
Patients with renal insufficiency require smaller than usual doses of digoxin. Newborn infants display considerable variability in their tolerance to digoxin, depending on their degree of maturity.
Premature and immature infants are particularly sensitive, and dosage must be reduced and digitalization should be even more individualized and cautiously approached than in more mature infants. Impaired renal function must also be carefully taken into consideration.
Congestive heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. A relatively low total dose administered in divided doses and concomitant use of antihypertensive drugs has been recommended. ECG monitoring is essential. Digoxin should be discontinued as soon as possible.
Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.
Patients with rheumatic carditis, especially when severe, are unusually sensitive to digoxin and prone to disturbances of rhythm. If heart failure develops, digitalization may be initiated with relatively low doses; then it can be cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.
Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS: Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid digoxin toxicity if digoxin is used to help the arrhythmia.
Digoxin is not indicated for the treatment of ventricular tachycardia unless congestive heart failure supervenes after a protracted episode not itself due to digoxin.
Potassium depletion sensitizes the myocardium to digoxin and toxicity may develop even with usual dosage. Hypokalemia may also alter the rate of onset and intensity of the positive inotropic effect of digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin.
Potassium wastage may result from diuretic or corticosteroid therapy, hemodialysis, and from suction of gastrointestinal secretions. It may accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing congestive heart failure. In general, rapid changes in serum potassium or other electrolytes are to be avoided, and intravenous treatment with potassium should be reserved only for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES section).
Patients with acute myocardial infarction, severe pulmonary disease, or far advanced heart failure may be more sensitive to digoxin and more prone to disturbances of rhythm.
Calcium affects contractility and excitability of the heart in a manner similar to that of digoxin. Calcium may produce serious arrhythmias in digitalized patients.
In myxedema, the digoxin requirements are less because excretion rate is decreased and blood levels are significantly higher.
In incomplete A-V block, especially in patients subject to Stokes-Adams attacks, advanced or complete heart block may develop if digoxin is given. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.
Patients with chronic constrictive pericarditis may respond unfavorably to digoxin.
Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.
Renal insufficiency delays the excretion of digoxin and dosage must be adjusted accordingly in patients with renal disease. Note: This applies also to potassium administration should it become necessary.
Electrical conversion of arrhythmias may require reduction of digoxin dosage.
Dosage must be carefully titrated and differences in the bioavailability of parenteral preparations, elixirs, and tablets should be taken into account when switching patients from one preparation to another.
Electrocardiographic monitoring may be necessary to avoid intoxication.
Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

ADVERSE REACTIONS:
Gynecomastia: Uncommon.

Overdose or toxic effects in adults:
Gastrointestinal: Anorexia, nausea, vomiting, diarrhea are the most common early symptoms of overdosages in the adult (but rarely conspicuous in infants). Uncontrolled heart failure may also produce such symptoms.
Central nervous system: Visual disturbances (blurred vision, yellow vision), headache, weakness, apathy.
Cardiac disturbances (arrhythmias): Ventricular premature beats are the most common, except in infants and young children. Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (interference) dissociation and paroxysmal atrial tachycardia (PAT) with block are also common arrhythmias due to digoxin overdosage.
Conduction disturbances: Excessive slowing of the pulse is a clinical sign of digoxin overdosage. Atrioventricular block of increasing degree may proceed to complete heart block. Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac toxic disturbances. Digoxin may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

Overdose or toxic effects in children:
Toxic signs differ from the adult in a number of respects. Cardiac arrhythmias are the more reliable and frequent signs of toxicity.
Vomiting and diarrhea, neurologic and visual disturbances are rare as initial signs.
Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.
Atrial arrhythmias, atrial ectopic rhythms, and paroxysmal atrial tachycardia with A-V block particularly are more common manifestations of toxicity in children.
Ventricular arrhythmias are rare.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE: Digoxin should be discontinued until all signs of toxicity are abolished. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.
Potassium salts are commonly used. Potassium chloride in divided oral doses totaling 4-6 grams for adults (see PEDIATRIC INFORMATION section for pediatric dosage) may be given provided renal function is adequate.
When correction of the arrhythmia is urgent and the serum potassium level is low or normal, potassium should be administered intravenously in a solution of 5 percent dextrose in water. A total of 40-100 milliequivalents (30 milliequivalents per 500 milliliters) is given at the rate of 20 milliequivalents per hour unless limited by pain due to local irritation.
Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.
Continuous electrocardiographic monitoring should be performed to watch for any evidence of potassium toxicity, e.g., peaking of T waves, and to observe the effect on the arrhythmia so that the infusion may be promptly stopped when the desired effect is achieved.

Caution: Potassium should not be used and may be dangerous for severe or complete heart block due to digoxin and not related to any tachycardia.
Other agents that have been approved for the treatment of digoxin intoxication include procainamide, lidocaine, and propranolol.

Pediatric Information: (See adult section for other recommendations for the treatment of arrhythmias produced by overdosages and for additional recommendations and cautions regarding the use of potassium.) Potassium preparations may be given orally in divided doses totaling 1-1.5 milliequivalents/kilogram (1 gram K contains 13.4 milliequivalents). When correction of the arrhythmia is urgent, approximately 0.5 milliequivalents/kilogram of potassium per hour may be given, with careful electrocardiographic monitoring, as a solution of 20 milliequivalents or less for 500 milliliters in 5 percent dextrose in water. The total dose should generally not exceed 2 milliequivalents of potassium/kilogram.

DOSAGE AND ADMINISTRATION: Oral digoxin is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. The amount can be predicted approximately from the lean body mass of the patient with allowances made for excretion during the time taken to induce digitalization.
Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.
Recommended dosages are practical average figures that may require considerable modification as dictated by individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended or average doses. (See WARNINGS and PRECAUTIONS sections.)
The average amount of digoxin that patients must accumulate to be digitalized with digoxin tablets is 1.0-1.5 milligrams. Digitalization may be accomplished by any of several approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount accumulated.
In previously undigitalized patients, a single loading dose of 0.5-0.75 milligram orally usually produces a detectable effect in 1-2 hours that becomes maximal in 6-8 hours. Additional doses of 0.25-0.5 milligram may be given cautiously at 6-8 hour intervals to full digitalization.
In previously undigitalized patients, institution of daily maintenance therapy (0.125-0.5 milligram, see next paragraph) without a loading dose results in development of steady-state plateau concentrations in about 7 days in patients with normal renal function.
The average daily oral maintenance dose is 0.125-0.5 milligram, usually 0.25 milligram. In the elderly patient, 0.125-0.25 milligram should be considered the average maintenance dose.
In patients with renal impairment, digoxin excretion is impaired and serum half-life is prolonged. Digitalizing and maintenance doses are lower than those recommended for patients with normal renal functions. Signs of digoxin toxicity develop sooner in patients with renal impairment, and it takes longer for toxic signs and symptoms to disappear. Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state plateau in patients with renal impairment than in patients with normal renal function.
It cannot be overemphasized that the values given are averages and substantial individual variation can be expected.

Children: Digitalization must be individualized. Generally, premature and immature infants are particularly sensitive, requiring reduced dosage that must be determined by careful titration.
Oral Dosage. Beyond the immediate newborn period, children require proportionally greater doses than adults on the basis of body weight or surface area. The recommended oral digitalizing dosages in children with normal renal function are:
Newborn infants (normal), up to 1 month, require 40-60 micrograms (mcg)/kilogram.
Infants, 1 month to 2 years, require approximately 60-80 micrograms (mcg)/kilogram.
Children, 2 years to 10 years, require 40-60 micrograms (mcg)/kilogram.
Children, over 10 years of age, require adult dosages in proportion to their body weight.
Maintenance therapy is 20-30 percent of the digitalizing dose administered each day.
Long term use of digoxin is indicated in almost all infants who have been digitalized for acute congestive heart failure unless the cause is transient. Many favor maintaining digoxin until at least 2 years of age in all infants with paroxysmal atrial tachycardia or in those who show either definite or latent failure.
Many children with severe inoperable congenital defects need digoxin throughout childhood and often for life.

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CLINICAL STUDIES

Electrophysiologic Evidence for Selective Retrograde Utilization of a Specialized Conducting System in Atrioventricular Nodal Reentrant Tachycardia

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In 12 patients with atrioventricular (A-V) nodal reentrant tachycardia, the existence and utilization of retrograde ventriculoatrial bypass tracts in the reentrant process were excluded, and the characteristics of the anterograde and retrograde limbs of the reentrant circuits were studied using His bundle electrograms, incremental atrial and ventricular pacing and atrial and ventricular extrastimulus techniques before and after the administration of 0.01 mg/kg of intravenous ouabain. Similar studies were also performed in five control patients without tachycardia. Paroxysmal supraventricular tachycardia could be induced in all 12 patients during atrial pacing-induced A-V nodal Wenckebach periods or premature atrial stimulation, or both. On the basis of conduction time in the retrograde limb during tachycardia and during retrograde studies, two groups were identified. Group I (seven patients) had (1) short (39 ± 10 msec) and constant conduction time in the retrogarde limb measured from the anterograde His bundle deflection to the retrograde atrial echo response (H-Ae interval), (2) no change in ventriculoatrial conduction time up to maximal ventricular pacing rates, (3) H_2-A_2 intervals during retrograde refractory period studies that were identical to the H-Ae intervals and that did not increase with decreasing V_1-V_2 intervals, and (4) increased conduction time of the anterograde limb (Ae-H intervals) after the administration of ouabain without any effect on retrograde limb conduction (H-Ae and H_2-A_2 intervals) and refractoriness. Group II (five patients) had (1) long and variable H-Ae intervals (60 to 180 msec), (2) a progressive increase in ventriculoatrial intervals during incremental ventricular pacing, (3) an increase in H_2-A_2 intervals in response to decreasing V_1-V_2 intervals, and (4) increased anterograde (Ae-H interval) and retrograde limb (H-Ae and H_2-A_2 intervals) conduction and refractoriness after the administration of ouabain. Changes in the H_2-A_2 interval corresponded to the changes in four of the five control patients. These findings suggest that (1) in group I the anterograde limb was the A-V node, whereas the retrograde limb was an A-V nodal bypass tract or an insulated intranodal tract physiologically unlike the A-V node; and (2) in group II the A-V node comprised both the anterograde and retrograde limbs of the reentrant circuit.

From the Cardiology Department, U.S. Public Health Service Hospital, Staten Island, New York. This work was supported in part by the Bureau of Medical Services and Project HL 12536-07 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received October 3, 1978; revised manuscript received November 20, 1978, accepted November 21, 1978.

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TABLE I

Conduction Characteristics of the Anterograde and Retrograde Limbs

Case no.	Cycle Length During PSVT (msec)				H-Ae Intervals (msec)				Ae-H Intervals (msec)	
	Control		Post-Ouabain		Control		Post-Ouabain		Control	
	Range	Av	Range	Av	Onset of H	End of H	Onset of H	End of H	Range	Av
					Group I					
1	280–310	295	330	330	30	15	30	15	250–280	265
2	310–315	314	320–325	322	30	15	30	15	280–285	284
3	275–300	288	340–350	345	50	35	50	35	230–250	238
4	330–370	354	360–370	368	50	30	50	30	280–320	308
5	430–450	440	445–460	450	50	30	50	30	385–405	395
6	305	305	320	320	35	20	35	20	270	270
7	340–400	363	. . .	. . .	30	15	30	15	310–370	333
					Group II					
8	560–630	600	640–640	645	173	143	185	155	395–445	426
9	390–395	391	415–420	417	60	40	65	45	330–335	331
10	285–300	293	335–350	342	80	60	87	65	195–215	210
11	575–625	600	680–685	683	125	105	186	160	450–500	475
12	430	430	430–465	440	71	50	96	75	360–365	361

Av = average; Post-Ouabain = after the administration of ouabain; PSVT = paroxysmal supraventricular tachycardia.

Reentry within the atrioventricular (A-V) node is acknowledged as a possible mechanism of paroxysmal supraventricular tachycardia.[1–5] In A-V nodal reentry, it is postulated that the anterograde limb of the reentrant circuit is characterized by slow conduction and a short refractory period, whereas the retrograde limb is characterized by fast conduction and a long refractory period.[6–11] With few exceptions,[11–13] recent studies[2–10] assessed conduction characteristics and refractoriness of the reentrant limb during anterograde studies, which is appropriate for study of the anterograde limb; however, it appears appropriate to study the properties of the retrograde limb during retrograde studies.

The purpose of this paper is to describe two groups of patients with paroxysmal supraventricular tachycardia due to reentry involving the region of the A-V node who demonstrated different electrophysiologic characteristics of the retrograde limb during tachycardia and during retrograde studies. The results suggest that in some patients the retrograde limb of the reentrant pathway may be an A-V nodal bypass tract, whereas in others it may be the A-V node. In addition, the effects of digitalis (a drug well known to increase A-V nodal conduction time and refractoriness[14–15] without appreciable effects on the His-Purkinje system)[16] on anterograde and retrograde conduction characteristics supported our findings.

Methods

Patients: Twelve patients with a history of palpitations and paroxysmal supraventricular tachycardia documented with electrocardiography and 5 control patients without tachycardia were studied. Their ages ranged from 30 to 76 years. Two patients had atherosclerotic heart disease, one had hypertension and the remaining patients had no evidence of heart disease. No patient had acute myocardial infarction or ischemia, electrolyte or metabolic abnormalities or the Wolff-Parkinson-White syndrome, and none received any cardioactive medication for at least 7 days before the study. The experimental nature of the procedure was explained to all patients and signed consent was obtained.

Procedures: Three quadripolar catheters were introduced percutaneously and fluoroscopically positioned in the high right atrium at the level of the tricuspid valve for recording His bundle activity[17] and in the right ventricular apex. Whenever possible an additional quadripolar catheter was positioned in the mid region of the coronary sinus. The proximal poles of the catheters were used for recording local electrical activity and the distal poles for stimulation. Two or more standard electrocardiographic leads, intracardiac electrograms (filtered at frequency settings of 40 to 500 Hz) and time lines generated at 10, 100 and 1,000 msec were displayed on a multichannel oscilloscope and recorded on magnetic tape. These tapes were subsequently replayed and reproduced on photographic paper at a speed of 150 mm/sec.

Atrial and ventricular pacing was performed up to the onset of anterograde and retrograde Wenckebach periods or up to heart rates of 160 to 200 beats/min. For anterograde and retrograde refractory period studies, comparable atrial (A_1-A_1) and ventricular (V_1-V_1) cycle lengths were scanned with extrastimuli (A_2 or V_2) after every eighth beat at progressively decreasing (by 10 msec) coupling intervals until atrial and ventricular muscle refractoriness. After the control studies were completed, ouabain, 0.01 mg/kg, was administered intravenously to all patients, and studies were repeated 30 minutes later.

Definition of Terms

The Ae-H interval was measured from the onset of the atrial echo (on the His bundle electrogram) to the onset of the His bundle deflection during sustained paroxysmal supraventricular tachycardia or during two or more echoes, or both. The Ae-H interval was used as a measure of conduction in the anterograde limb of the reentry circuit. *The H-Ae interval* was measured from the onset and the end of the His bundle deflection to the onset of the atrial echo (on the His bundle electrogram) during sustained supraventricular tachycardia or during induced echoes, or both. This interval was used as a measure of conduction in the retrograde limb of the reentry circuit. *H-Ae:Ae-H* was the ratio of these two intervals. Akhtar et al.[13] recently reported that this ratio is useful in localizing

TABLE I
continued

Case no.	Ae-H Intervals (msec) Post-Ouabain Range	Ae-H Intervals (msec) Post-Ouabain Av	H-Ae:Ae-H Ratio Control Range	H-Ae:Ae-H Ratio Post-Ouabain Range	Retrograde H_2-A_2 Intervals (msec) Control Onset of H	Control End of H	Post-Ouabain Onset of H	Post-Ouabain End of H
				Group I				
1	300	300	1:8.33–9.33	1:10	30	15	30	15
2	290–295	292	1:9.33–9.5	1:9.66–9.83	30	15	30	15
3	295–300	297	1:4.6–5	1:5.9–6.0	50	35	50	35
4	310–320	318	1:5.6–6.4	1:6.2–6.4	50	30	50	30
5	395–410	402	1:7.7–8.1	1:7.9–8.2	50	30	50	30
6	285	285	1:7.7	1:8–10	35	20	35	20
7	. . .	. . .	1:10.3–12.3	. . .	30	15	30	15
				Group II				
8	465–470	467	1:2.39–2.4	1:2.5–2.54	150–200	130–180	185–215	165–195
9	350–360	356	1:5.4–5.58	1:5.38–6.0	60–70	45–55	65–70	55–58
10	260–265	261	1:2.43–2.68	1:2.88–3.05	70	55–60	80–90	70–80
11	480–510	495	1:3.6–4.	1:2.4–2.9	420–440	400–420	Block	Block
12	290–370	360	1:4.86–5.14	1:1.65–5.28	70–80	50–55	70–90	50–70

the site of reentry. *Anterograde refractory periods* were defined as described previously.[18]

Retrograde conduction intervals: The ventriculoatrial interval was measured from the stimulus artifact during incremental ventricular pacing to the onset of the retrograde low atrial electrogram. *The H_2-A_2 interval* was measured from the onset and the end of the His bundle deflection during premature ventricular stimulation to the onset of the retrograde atrial electrogram on the His bundle tracing.

Retrograde refractory periods[16,19]**:** *The functional refractory period of the vetriculo-atrial conducting system* is the shortest A_1-A_2 interval in response to any range of V_1-V_2 intervals. *The functional refractory period of the A-V nodal region* is the shortest A_1-A_2 interval in response to two successive retrograde impulses both conducted from the His bundle. *The functional refractory period of the His-Purkinje system* is the shortest V_1-H_2 or H_1-H_2 interval in response to any range of V_1-V_2 intervals. *The effective refractory period*

TABLE II

Anterograde and Retrograde Conduction Patterns

Case no.	Sinus CL (msec) Control	Sinus CL (msec) Post-Ouabain	A-H (msec) Control	A-H (msec) Post-Ouabain	H-V (msec) Control	H-V (msec) Post-Ouabain	ACL for A-V Nodal WB (msec) Control (msec)	ACL for A-V Nodal WB (msec) Post-Ouabain	Retrograde Conduction (msec) Control	Retrograde Conduction (msec) Post-Ouabain
					Group I					
1	740	850	60	65	35	35	300	310	1:1 VA up to VCL 355	1:1 VA up to VCL 355
2	580	660	100	105	50	50	300	300	1:1 VA up to VCL 300	1:1 VA up to VCL 300
3	655	840	75	75	35	35	360	370	WB at VCL 375	WB at VCL 375
4	680	710	75	85	40	40	340	350	1:1 VA up to VCL 3 0	1:1 VA up to VCL 370
5	960	1,000	110	130	40	40	440	460	WB at VCL 460	WB at VCL 460
6	830	960	80	85	50	50	400	400	1:1 VA up to VCL 380	1:1 VA up to VCL 380
7	610	680	55	60	40	40	370	380	1:1 VA up to VCL 300	1:1 VA up to VCL 300
					Group II					
8	770	1,100	95	95	50	50	545	650	WB at VCL 500	WB at VCL 500
9	735	630	95	110	55	55	400	450	1:1 VA up to VCL 370	1:1 VA up to VCL 370
10	990	1000	100	110	55	55	300	350	1:1 VA up to VCL 350	1:1 VA up to VCL 350
11	600	610	100	125	50	50	400	430	WB at VCL 430	VA block at VCL 500
12	1,090	1,100	115	115	40	40	400	400	WB at VCL 460	WB at VCL 460

ACL = atrial cycle length; CL = cycle length; Post-Ouabain = after the administration of ouabain; VA = ventriculoatrial conduction; VCL = ventricular length; WB = Wenckebach block.

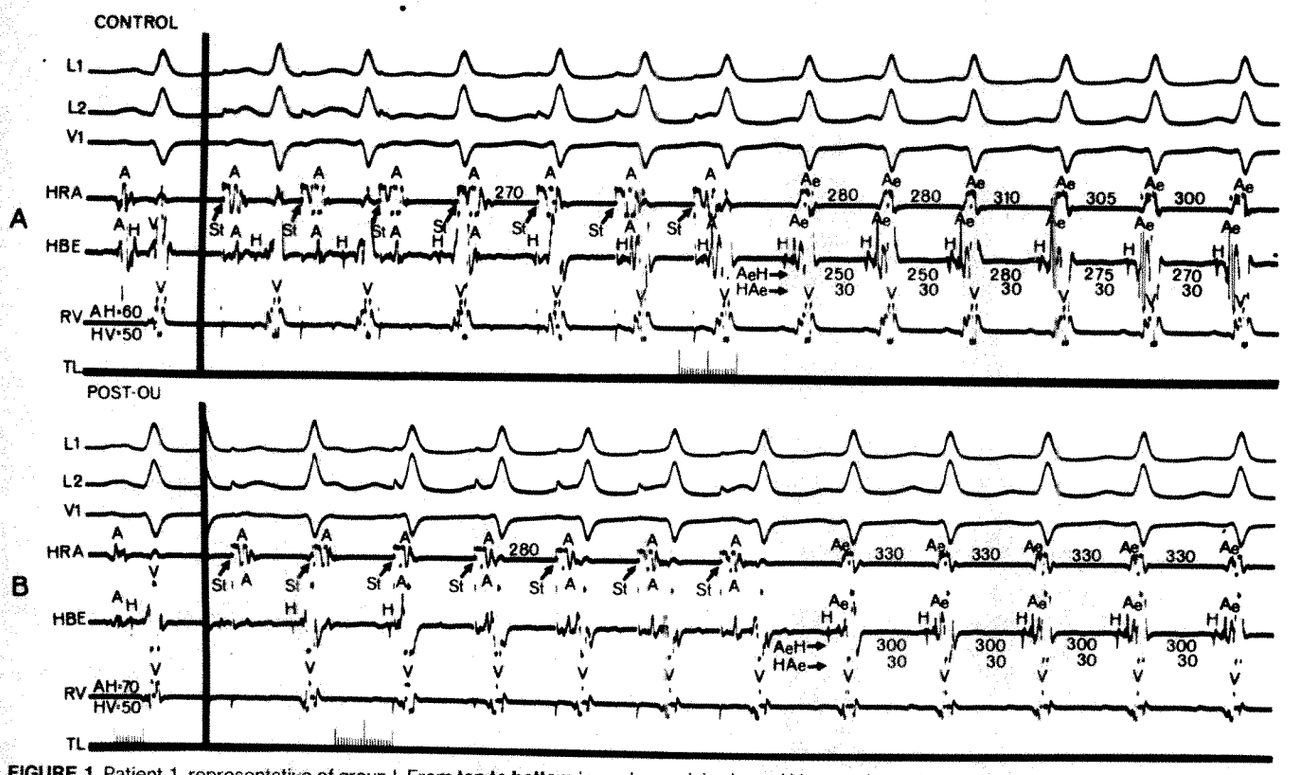


FIGURE 1. Patient 1, representative of group I. From **top to bottom** in each panel, L_1, L_2 and V_1 = surface electrocardiographic leads I, II and V_1; HRA = high right atrial electrogram; HBE = His bundle electrogram; RV = right ventricular electrogram; TL = time lines generated at 10, 100 and 1,000 msec. **Panel A,** control tracings demonstrating the initiation of paroxysmal supraventricular tachycardia during atrial pacing. During atrial pacing (St = atrial stimuli), there was a progressive increase in A-H intervals. When the pacing was interrupted, paroxysmal supraventricular tachycardia ensued. The cycle length during tachycardia (Ae-Ae intervals) ranged from 280 to 310 msec. The Ae-H interval varied from 250 to 280 msec, whereas the H-Ae interval, which was markedly short (30 msec), remained unchanged. The spontaneous variation in cycle length of the tachycardia was primarily related to variations in Ae-H intervals. Note that the atrial echo beat (Ae) on the His bundle electrogram occurred before the ventricular electrogram so that the H-Ae interval (30 msec) was shorter than the H-V interval (50 msec). **Panel B,** tracings after the administration of ouabain (POST-OU) demonstrating the initiation of paroxysmal supraventricular tachycardia during atrial pacing. After ouabain, the cycle length of the tachycardia increased (Ae-Ae = 330 msec), that is, the rate of tachycardia decreased. Note that the increase in cycle length was primarily related to an increase in Ae-H intervals (300 msec), whereas the H-Ae interval (30 msec) was similar to the control value (**panel A**).

of the ventriculoatrial conducting system is the longest V_1-V_2 interval at which V_2 fails to evoke an A_2 response. *The effective refractory period of the A-V nodal region* is the longest V_1-H_2 or H_1-H_2 interval at which H_2 (retrograde His bundle depolarization) is not followed by an A_2. *The effective refractory period of the His-Purkinje system* is the longest V_1-V_2 interval that does not evoke an H_2 response (block in both bundle branches). This interval can be assessed only if H_2 is identified before block.

Discontinuous A-V nodal curves: The presence of discontinuous A-V nodal curves during anterograde studies was demonstrated by plotting the A_1-A_2 and the corresponding H_1-H_2 responses as previously described.[8,9] The presence of discontinuous curves during retrograde studies was demonstrated by plotting the V_1-V_2 intervals and the corresponding retrograde A_1-A_2 and H_2-A_2 intervals.

Statistical analysis was performed using Student's *t* test for paired and unpaired data. All values are expressed as mean values ± standard deviations.

Results

Paroxysmal supraventricular tachycardia could be induced in all 12 patients during atrial pacing-induced A-V nodal Wenckebach periods or during premature atrial stimulation, or both. The reentrant nature of these arrhythmias was suggested by (1) the initiation and termination of tachycardia by a single or two consecutive atrial stimuli; (2) the initiation of tachycardia or atrial echoes, or both, at critical A-H delays; and (3) a retrograde or reversed atrial activation sequence during tachycardia or during induced echoes, or both. The patients were classified into two groups on the basis of the H-Ae intervals and the ventriculoatrial conduction patterns during control studies.

Group I patients (Cases 1 to 7, Tables I and II) demonstrated (1) short H-Ae intervals that averaged 39 ± 10 msec (range 30 to 50 msec) when measured from the onset of the His bundle deflection and 23 ± 9 msec (range 15 to 30 msec) when measured from the end of the His bundle deflection, (2) H-Ae intervals that remained constant despite changes in the rate of tachycardia and changes in the Ae-H intervals, (3) no change in ventriculoatrial conduction time during maximal paced ventricular rates with 1:1 intact ventriculoatrial conduction or up to the onset of retrograde ventriculoatrial block, and (4) H_2-A_2 intervals during retrograde

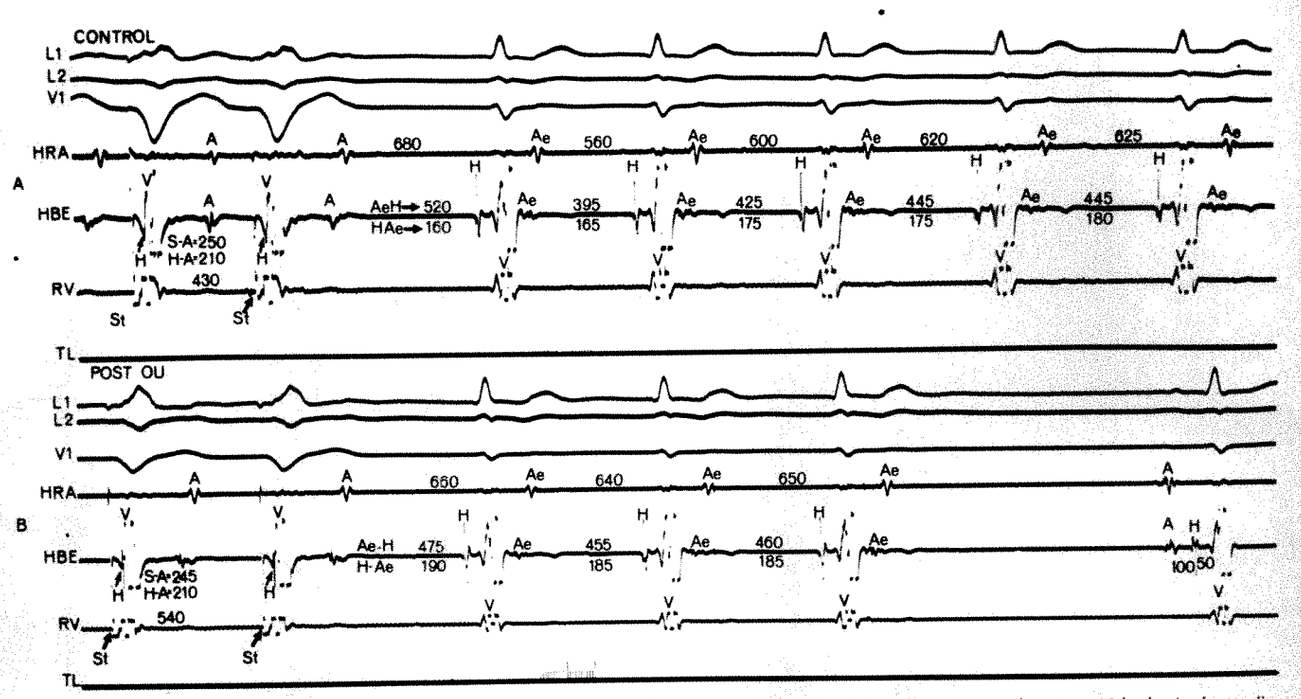


FIGURE 2. Patient 8, representative of group II. **Panel A,** control tracings demonstrating the initiation of paroxysmal supraventricular tachycardia during the interruption of ventricular pacing. During ventricular pacing at a cycle length of 430 msec, 1:1 V-A response occurred. The stimulus-A (S-A) interval was 250 msec and the H-A interval 210 msec. When the stimulus was omitted after the second paced beat, paroxysmal supraventricular tachycardia was initiated without prior prolongation of the H-A interval. The cycle length of the tachycardia ranged from 560 to 625 msec. The Ae-H interval (395 to 445 msec) and also the H-Ae interval (165 to 180 msec) demonstrated spontaneous variations. Note that the atrial echo (Ae) response on the His bundle electrogram occurred after the local ventricular electrogram in the S-T segment. **Panel B,** during ventricular pacing at a cycle length of 540 msec, 1:1 ventriculoatrial response occurred. Note, however, that the H-A interval was 210 msec at a ventricular pacing cycle length of 540 msec. Paroxysmal supraventricular tachycardia was initiated when the stimulus was omitted, with the cycle length of tachycardia 640 to 650 msec. Note that both the Ae-H interval (445 to 460 msec) and the H-Ae interval (185 msec) increased after the administration of oubain (POST OU). Also, paroxysmal supraventricular tachycardia could no longer be sustained and terminated in the anterograde limb of the reentrant circuit. Abbreviations as in Figure 1.

refractory period studies that were identical to the H-Ae intervals and that did not increase with decreasing V_1-V_2 intervals.

Group II patients (Cases 8 to 12, Tables I and II) demonstrated: (1) H-Ae intervals of 60 to 180 msec when measured from the onset of the His bundle deflection, much longer than those in group I patients; (2) variations in H-Ae intervals during tachycardia; (3) a progressive increase in ventriculoatrial intervals during incremental ventricular pacing; and (4) increases in the H_2-A_2 interval in response to decreasing V_1-V_2 intervals during retrograde refractory period studies.

Conduction Patterns

Conduction in the anterograde and retrograde limbs of the reentry circuit (Table I): *Group I:* During control studies, the Ae-H intervals ranged from 265 to 395 msec and increased in duration (293 ± 54 to 315 ± 44 msec, P <0.05) after the administration of ouabain in all patients in whom these intervals could be compared with control values. In contrast, the H-Ae intervals, which were significantly (P <0.001) and markedly shorter than the corresponding Ae-H intervals (H-Ae:Ae-H = 1:4.1 to 1:12.3), did not change after the administration of ouabain (Fig. 1). The H-Ae:Ae-H ratios (1:7.23 ± 1.69 to 1:7.94 ± 1.69, P <0.05) and cycle length (Ae-Ae intervals) of tachycardia (337 ± 57 to 356 ± 52 msec, P <0.05) also increased significantly after the administration of ouabain.

Group II: The Ae-H interval during control studies ranged from 210 to 475 msec and, as in group I, increased significantly after the administration of ouabain (361 ± 101 to 388 ± 94 msec, P <0.05). In contrast to the findings in group I patients, the range of H-Ae intervals also increased (average increase +22 msec) after the administration of ouabain (Fig. 2). The H-Ae:Ae-H ratios, which were smaller than those in group I (1:3.7 ± 1.3 versus 1:7.67 ± 2.01, P <0.005) did not change significantly after the administration of ouabain from 1:3.96 ± 1.42 to 1:3.95 ± 1.57, P not significant; upper limits of H-Ae:Ae-H ratios). Increases in the cycle length of tachycardia after the administration of ouabain (463 ± 136 to 506 ± 151 msec, P <0.025) were related to increases in both the Ae-H and H-Ae intervals. The longer Ae-H and H-Ae intervals in the group II patients contributed to the significantly longer cycle length of tachycardia than in the group I patients (463 ± 136 versus 337 ± 54 msec, P <0.05).

Echo zones and the ability to sustain tachycardia: An echo zone was defined only when atrial echoes could

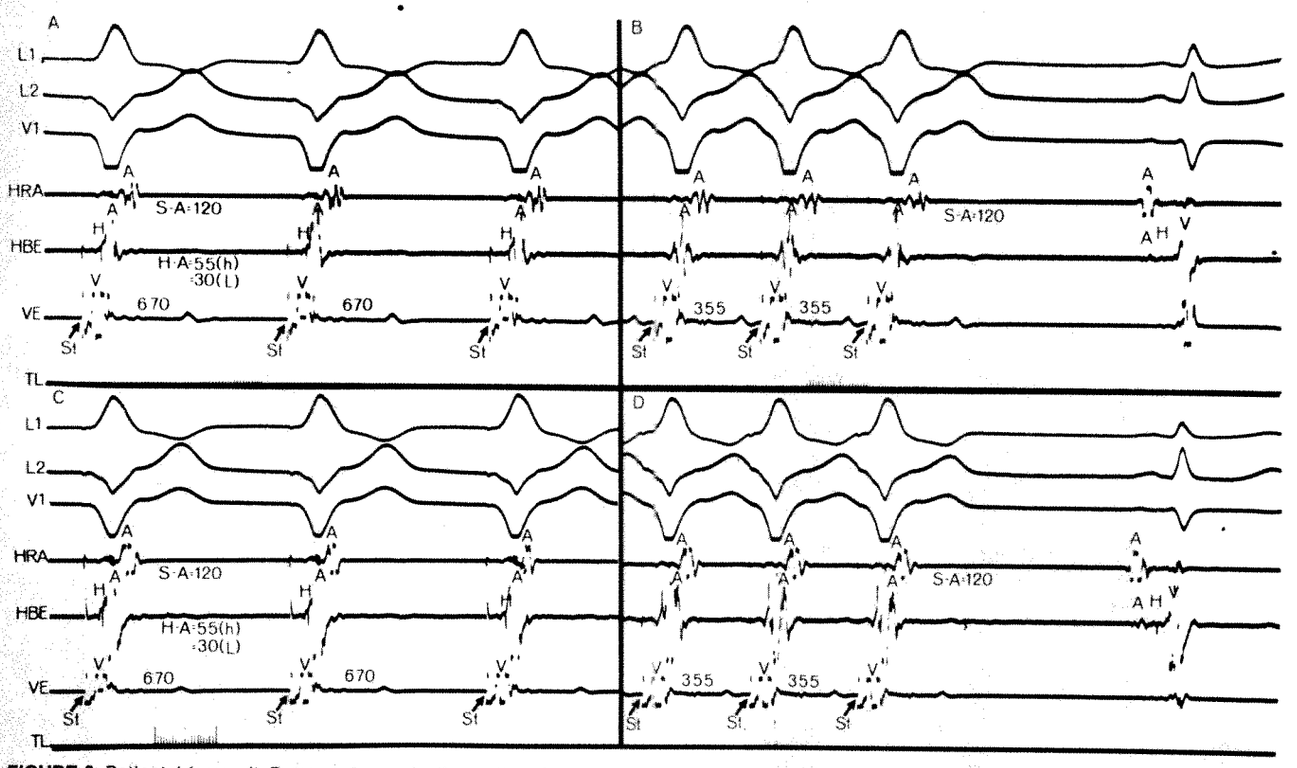


FIGURE 3. Patient 1 (group I). Retrograde conduction pattern in control tracings (**A** and **B**) and after the administration of ouabain (**C** and **D**). **Panel A,** the right ventricle (VE) was paced at a cycle length of 670 msec. The S-A interval was 120 msec, whereas the H-A (high) interval was 55 msec and the H-A (low) interval 30 msec. **Panel B,** there was a 1:1 V-A response during ventricular pacing at a cycle length of 355 msec (175 beats/min). Also, note that the S-A interval did not change at the maximal pacing rate. **Panels C and D,** after the administration of ouabain, the ventriculoatrial response during ventricular pacing at comparable cycle lengths was similar to the control findings. Abbreviations as in Figure 1.

be induced over two or more coupling intervals (A_1-A_2). Although atrial echoes could be induced in all 12 patients during anterograde refractory period studies, echo zones could be delineated in 4 of 7 patients in group I and in 3 of 5 patients in group II. In the remaining patients, the attainment of the effective refractory period of the A-V node limited the delineation of an echo zone.

Group I: Echo zones ranged from 10 to 220 msec. After the administration of ouabain, the echo zone was abolished in one patient (Case 6) and decreased 20 to 60 msec in the remaining three patients (Cases 3, 5, and 7). The ability to sustain tachycardia was lost in two of five patients due to block in the anterograde limb of the reentrant circuit (that is, Ae-H block).

Group II: Echo zones ranged from 35 to 60 msec in duration. After the administration of ouabain, the duration of the echo zones decreased in two patients (Cases 9 and 10; range −15 to −20 msec) and increased in two patients (Cases 11 and 12; range +10 to +40 msec). In three patients (Cases 9, 10 and 11) the echo zones shifted to the right. The ability to sustain tachycardia was lost in two of four patients (Fig. 2) due to block in the anterograde limb of the reentrant circuit.

Anterograde and retrograde conduction patterns (Table II): *Group I:* During incremental atrial pacing, A-V nodal conduction time (A-H intervals) increased progressively in all patients, with A-V nodal Wenckebach periods occurring at atrial cycle lengths of 360 ± 51 msec (range 300 to 440 msec). After the administration of ouabain, the A-H intervals during sinus rhythm and during atrial pacing were longer than the control values.

During incremental ventricular pacing the shortest ventriculoatrial intervals were 111 ± 13 msec (range 90 to 130 msec). After the administration of ouabain, the ventriculoatrial conduction patterns did not change (Fig. 3, Table II). Paroxysmal supraventricular tachycardia could not be induced in any of these patients during ventricular pacing and interruption of pacing.

Group II: A-V nodal Wenckebach periods occurred at an average atrial cycle length of 409 ± 87 msec (range 300 to 545 msec) and increased significantly ($P < 0.05$) after the administration of ouabain in four of five patients (456 ± 115 msec, range 350 to 650 msec).

During ventricular pacing, the shortest ventriculoatrial intervals ranged from 120 to 180 msec and were significantly longer than in group I (161 ± 39 versus 111 ± 13 msec, $P < 0.01$). Moreover, ventriculoatrial intervals (average +35 msec) increased progressively in all patients. In contrast to the results in group I, paroxysmal supraventricular tachycardia could be induced during interruption of ventricular pacing in three of five patients (Cases 8, 11 and 12) (Fig. 2). After the admin-

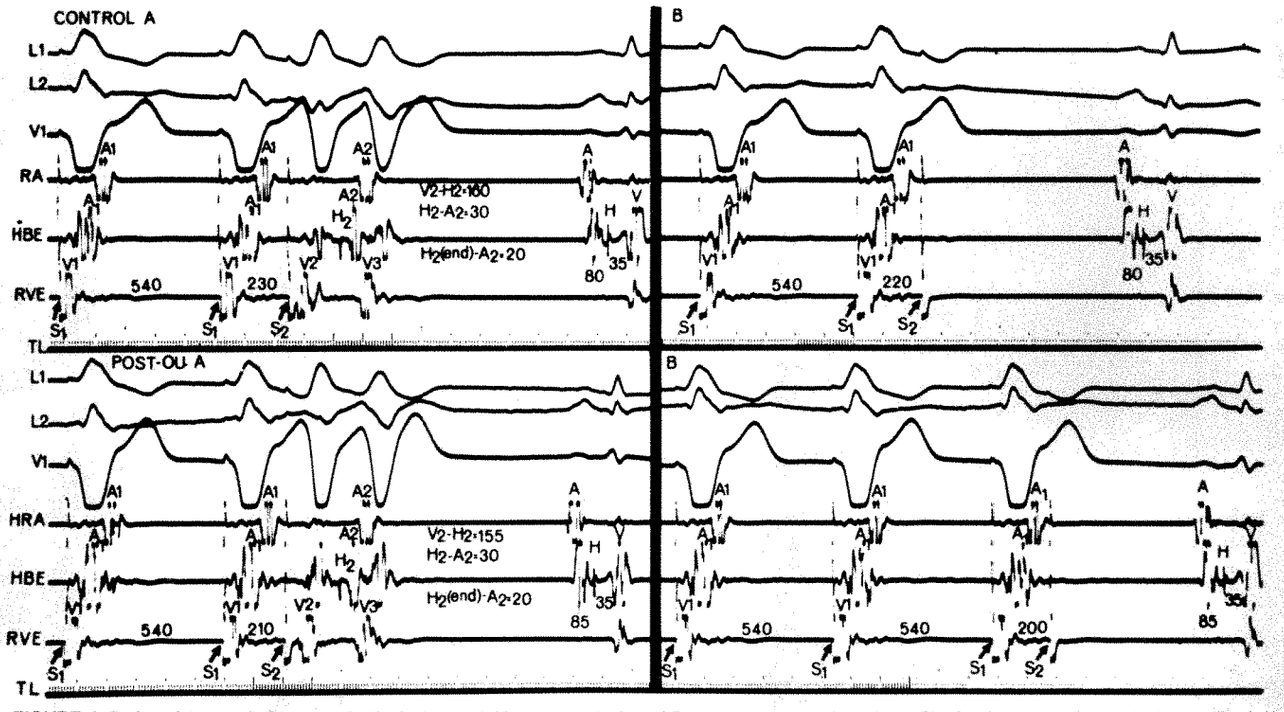


FIGURE 4. Patient 2 (group I). Retrograde H_2-A_2 interval. **Upper panels A and B** represent control tracings. The basic ventricular cycle length (S_1-S_1) was 540 msec in all panels. The retrograde His bundle deflection during the basic drive was obscured by the local ventricular electrogram. At an S_1-S_2 interval of 230 msec (**panel A**), S_2 was conducted to the atria with a V_2-H_2 interval of 160 msec and an H_2-A_2 interval of 30 msec when measured from the onset of the His bundle deflection and 20 msec when measured from the end of the deflection. Note that A_2 followed H_2, and V_2 was followed by a reentrant ventricular beat (V_3) from reentry within the His-Purkinje system. V_3 failed to retrogradely depolarize the atria due to block below the bundle of His. At an S_1-S_2 interval of 220 msec (**panel B**), the ventricular muscle was refractory. **Bottom panels A and B** represent tracings after the administration of ouabain (POST-OU). The ventricle was paced at a similar cycle length of 540 msec. At an S_1-S_2 interval of 210 msec (**panel A**), S_2 was conducted to the atria with a V_2-H_2 of 155 msec and an H_2-A_2 of 30 msec. Note that the H_2-A_2 interval when measured from either the onset or the end of the His bundle was similar to the control value (**upper panel A**) and did not increase after the administration of ouabain. At an S_1-S_2 interval of 200 msec (**panel B**), the ventricular muscle was refractory. Note that despite a decrease in ventricular muscle refractoriness (after ouabain) and the attainment of a shorter V_2-H_2 interval (155 msec) compared with the control value, the H_2-A_2 interval did not increase after ouabain. RVE = right ventricular electrogram; other abbreviations as in Figure 1.

istration of ouabain, ventriculoatrial block developed in only one patient (Case 11) at a ventricular cycle length of 500 msec; in the remaining four patients either block developed or 1:1 conduction was maintained at similar ventricular cycle lengths as during control and the ventriculoatrial intervals were longer than during control studies (Fig. 2).

H_2-A_2 intervals: During retrograde refractory period studies, the retrograde His bundle deflection for the basic drive beats (H_1) was usually obscured by the ventricular electrogram. However, at closer V_1-V_2 intervals, the retrograde His bundle deflection emerged from the V_2 electrogram in all patients and was followed by an A_2. For the entire series of patients (except Patient 11, see later) the retrograde H_2-A_2 intervals showed an excellent correlation with the H-Ae interval ($r = 0.997$, $P < 0.001$).

In group I, the retrograde H_2-A_2 intervals were identical to the H-Ae intervals and remained constant at decreasing V_1-V_2 intervals. Retrograde H_2-A_2 intervals were not affected by ouabain in this group of patients (Fig. 4, Table I). In Patient 11 of group II, the H_2-A_2 interval corresponded to the Ae-H interval (H_2-A_2 = 420 to 440 msec; Ae-H = 450 to 500 msec), suggesting that the slow pathway was utilized for retrograde conduction.

In four of five patients (group II), the H_2-A_2 intervals increased in duration by 5 to 20 msec after the administration of ouabain. In Patient 11, H_2 blocked in the A-V node at all V_1-V_2 and V_1-H_2 intervals.

Control patients: To further exclude any differential effects of ouabain on retrograde A-V nodal conduction, five patients without paroxysmal supraventricular tachycardia were similarly studied before and after the administration of ouabain. In three of four patients the H_2-A_2 intervals increased 5 to 30 msec, and in the fourth patient H_2-A_2 block developed at all V_1-H_2 and V_1-V_2 intervals after the administration of ouabain.

Anterograde and Retrograde Refractory Periods

Group I

Anterograde refractory periods: *During control studies,* the functional refractory period of the A-V node exceeded the functional, relative and effective refractory periods of the His-Purkinje system. The effective refractory period of the A-V node was attained

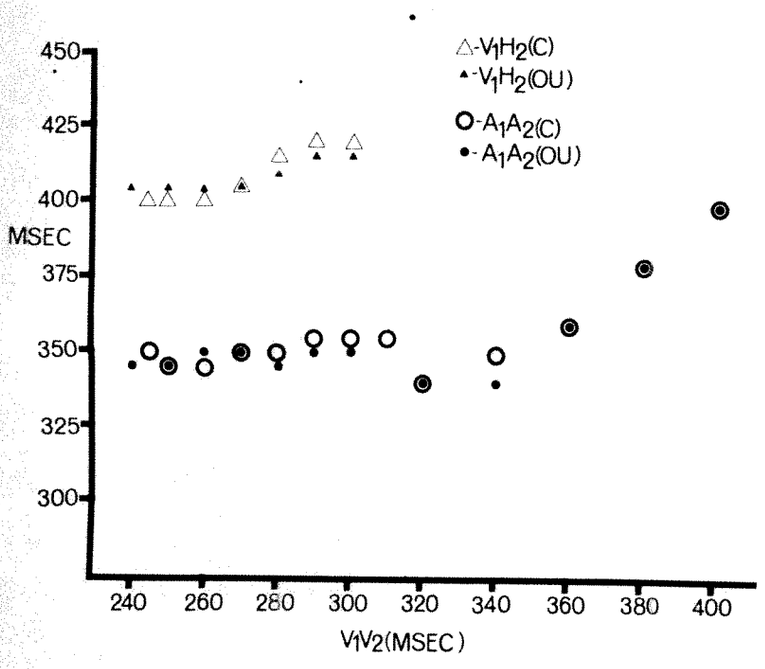


FIGURE 5. Group I. Retrograde functional refractory period pattern of the ventriculoatrial conducting system. The V_1-V_2 intervals (**abscissca**) are plotted against the A_1-A_2 and V_1-H_2 intervals (**ordinate**) during control (**C**) and after the administration of ouabain (OU). Note that initially with a progressive decrease in the V_1-V_2 interval, in the A_1-A_2 intervals decreased progressively. At about the time when H_2 emerged from the V_2 electrogram, the A_1-A_2 interval shifted upward. Note that the A_1-A_2 curve parallels the V_1-H_2 curve because delay occurred only within the His-Purkinje system (V_2-H_2). Thus, the functional refractory period of the ventriculoatrial conducting system was determined primarily by the His-Purkinje system. After the administration of ouabain (**solid circles**), note that the A_1-A_2 curves followed the control pattern (**open circles**).

in three of seven patients; in the remaining patients the effective refractory period of the atrium exceeded that of the A-V node. Discontinuous A-V nodal curves were not observed in any of these patients at one or more cycle lengths (A_1-A_2).

After the administration of ouabain, the duration of the functional refractory period of the A-V node increased in three patients. The duration of the effective refractory period of the A-V node increased in the three patients who attained this period during control studies.

Retrograde refractory periods: *During control studies,* the retrograde functional refractory period of the ventriculoatrial conducting system was determined by the His-Purkinje system because conduction delay occurred only below the His bundle (that is, V_2-H_2 delays). Furthermore the retrograde functional refractory period of the ventriculoatrial conducting system was shorter than that of the A-V conducting system (373 ± 24 versus 408 ± 51 msec). The retrograde effective refractory period of the A-V nodal region was not attained in any of these patients, whereas the retrograde effective refractory period of the His-Purkinje system could be determined in four of seven patients. Thus, the retrograde effective refractory period of the ventriculoatrial conducting system was determined by the His-Purkinje system. Paroxysmal supraventricular tachycardia could not be initiated in any of these patients during retrograde refractory period studies, and no retrograde discontinuous A-V nodal responses were observed.

After the administration of ouabain, there was no significant change in the retrograde functional refractory period of the A-V nodal region (386 ± 32 to 387 ± 33 msec, P not significant) or that of the ventriculoatrial conducting system (374 ± 24 to 371 ± 26 msec, P not significant) (Fig. 5). Also, as during control studies, no patient attained the effective refractory period of the A-V node.

Group II

Anterograde refractory periods: *During control studies,* as in group I, the functional refractory period of the A-V node was longer than the functional, relative and effective refractory periods of the His-Purkinje system in all five patients. The effective refractory period of the A-V node was attained in two patients (Cases 8 and 11); in the other three patients, the effective refractory period of the atrium exceeded that of the A-V node. Discontinuous A-V nodal response curves were observed in three of five patients (Cases 8, 9 and 11).

After the administration of ouabain, the functional refractory period of the A-V node (438 ± 66 to 480 ± 52 msec, $P < 0.005$) and that of the A-V conducting system increased significantly. The effective refractory period of the A-V node increased 70 to 120 msec in the two patients (Cases 8 and 11) in whom it could be determined during control studies and was attained in two other patients (Cases 9 and 11).

Retrograde refractory periods: In contrast to the findings in group I patients, the functional refractory period of the ventriculoatrial conducting system was determined by both the His-Purkinje system and the A-V node because conduction delay occurred both within the His-Purkinje system and the A-V node (V_2-H_2 and H_2-A_2 delays). Furthermore, the functional refractory period of the ventriculoatrial conducting system was similar to that of the A-V conducting system (434 ± 64 versus 428 ± 66 msec). As in group I patients, the effective refractory period of the A-V node was not attained in any patient. Retrograde discontinuous A-V nodal curves were observed in Patient II (Fig. 6). During retrograde studies in this patient, a reverse form of

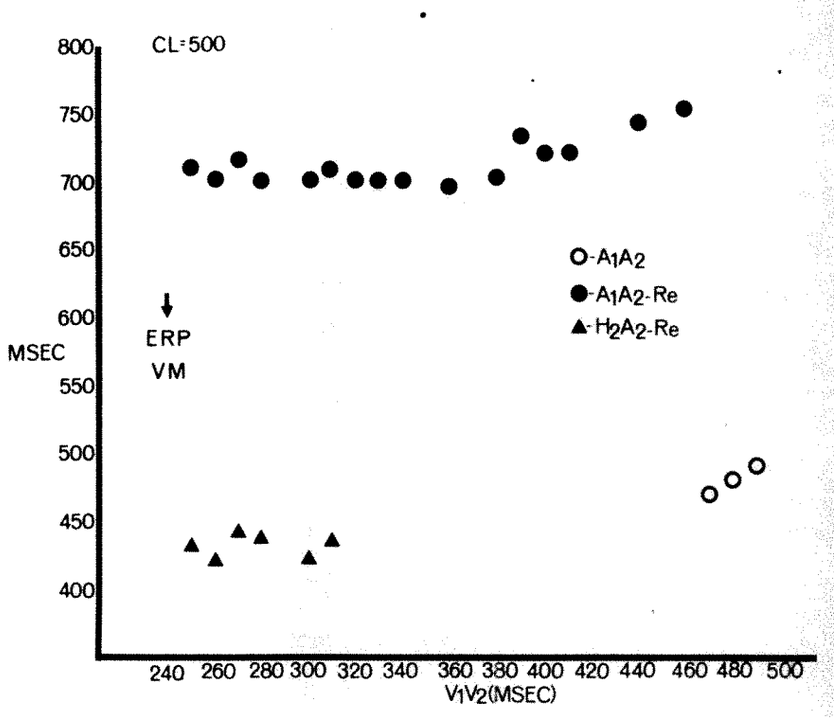


FIGURE 6. Patient 11 (group II). Retrograde discontinuous A-V nodal response curves. The V_1-V_2 intervals (**abscissa**) are plotted against the A_1-A_2 and H_2-A_2 intervals (**ordinate**). At a V_1-V_2 interval of 490 to 470 msec, the A_1-A_2 intervals (**open circles**) decreased progressively. At a V_1-V_2 interval of 460 msec, the A_1-A_2 interval jumped suddenly to 750 msec, suggesting failure in conduction in the retrograde fast pathway. Paroxysmal supraventricular tachycardia or atrial echo beats, or both, occurred on the retrograde slow pathway curve, suggesting that the slow pathway was utilized for retrograde conduction and the fast pathway for anterograde conduction. The H_2-A_2 intervals during retrograde (Re) slow pathway conduction ranged from 420 to 440 msec. CL = cycle length; ERP = effective refractory period.

tachycardia could be initiated with the slow conducting pathway being utilized for retrograde and the fast conducting pathway for anterograde conduction (Fig. 7).

After the administration of ouabain, the duration of the retrograde functional refractory period of the A-V node increased in two patients (Cases 9 and 12), did not change in one patient (Case 10) and decreased 10 msec in one patient (Case 8). In the latter patient, the decrease in the retrograde functional refractory period of the A-V node was related to a decrease in the retrograde functional refractory period of the His-Purkinje system, thus allowing the measurement of A_1-A_2 intervals at shorter V_1-H_2 intervals. The retrograde refractory period of the A-V node could not be assessed in Patient 11 due to retrograde A-V nodal block that also obviated the initiation of tachycardia utilizing the slow pathway for retrograde conduction.

Discussion

The electrophysiologic findings in the 12 patients in this study indicate that the site of reentry during paroxysmal supraventricular tachycardia was the region of the atrioventricular (A-V) node. The existence and utilization of ventriculoatrial bypass tracts in the reentrant process were excluded because (1) during retrograde refractory period studies, A_2 always followed H_2 by a constant or increasing H_2-A_2 interval (for any V_1-V_2 interval) and never preceded H_2; (2) conduction in the retrograde limb (H-Ae intervals) was independent of intraventricular conduction patterns[20]; (3) the H-Ae intervals were markedly and significantly shorter than the corresponding Ae-H intervals (H-Ae:Ae-H ratios 1:2.39 to 1:12.3)[13]; and (4) ventricular stimulation during sustained supraventricular tachycardia did not result in atrial preexcitation.[21,22]

Of interest were the observations on the H-Ae intervals and retrograde A-V nodal conduction patterns that permitted the classification of these patients into two groups. The effects of digitalis (a drug known to increase A-V nodal conduction and refractoriness)[10,12,14,15] on Ae-H and H-Ae intervals and on anterograde and retrograde A-V nodal conduction and refractoriness provided much useful information on the mechanism of paroxysmal supraventricular tachycardia in these patients.

Electrophysiologic characteristics of the anterograde and retrograde limbs of the reentry circuit: Control studies and those after the administration of ouabain in group I suggest that the anterograde limb of the reentry circuit was the A-V node but that the retrograde limb comprised a pathway with electrophysiologic characteristics unlike that of the A-V node. This hypothesis is supported by the observation that conduction time in the anterograde limb (Ae-H intervals) increased after the administration of ouabain. The increase in the cycle length of tachycardia and the H-Ae:Ae-H ratios after ouabain was solely related to the observed increase in anterograde conduction. Also, the response in A-V conduction (increase in A-H intervals with A-V nodal Wenckebach periods) to atrial pacing suggests that the A-V node was preferentially utilized for anterograde conduction.

Selective utilization of a pathway with electrophysiologic properties unlike that of the A-V node for retrograde conduction is suggested by the following: (1) The retrograde limb of the reentry circuit demonstrated short and constant conduction times (H-Ae intervals)

that were unaffected by changes in the rate of tachycardia, conduction in the anterograde limb and administration of ouabain. The effect of ouabain on the H-Ae intervals in group II and the retrograde H_2-A_2 intervals in control patients rules out the possibility of differential digitalis effects on anterograde versus retrograde A-V nodal conduction. (2) There was no change in ventriculoatrial conduction time during control studies or after the administration of ouabain, in contrast to the well known relation between decreases in cycle length and increases in refractoriness and conduction within the A-V node,[23,24] whereby in most patients the A-V node is the site of delay during incremental ventricular pacing.[19] This behavior of ventriculoatrial conduction is qualitatively similar to that described in patients with the Wolff-Parkinson-White syndrome and ventriculoatrial accessory pathways with utilization of the bypass tract for retrograde propagation.[25,26] Importantly, the retrograde H_2-A_2 intervals were constant and identical to the H-Ae intervals and similarly unaffected by ouabain. These findings indicate that the fast conducting pathway was selectively and solely utilized for retrograde conduction and the distal limb of this pathway was connected to the His bundle. (3) The functional and effective refractory periods of the ventriculoatrial conducting system were primarily

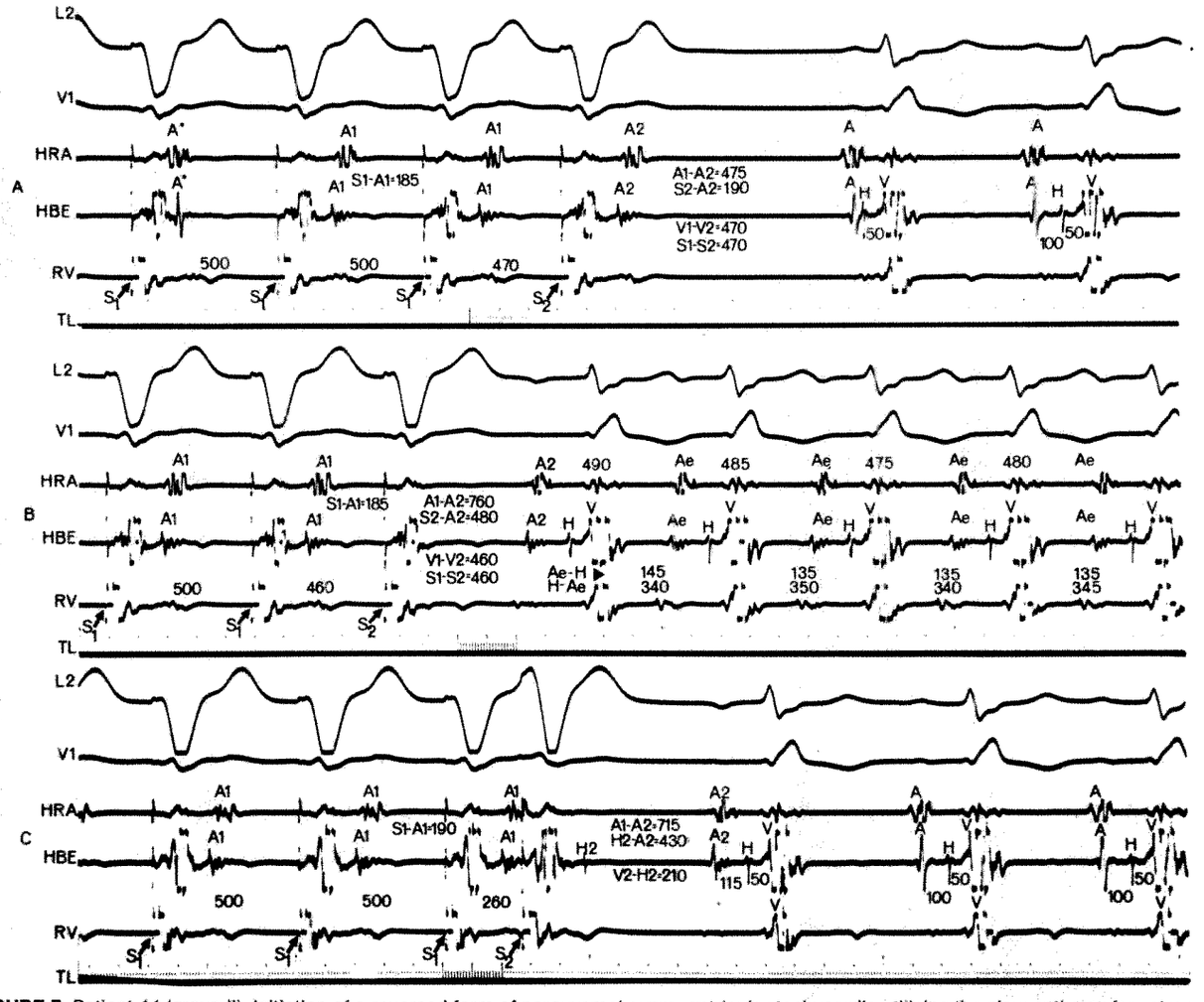


FIGURE 7. Patient 11 (group II). Initiation of a reversed form of paroxysmal supraventricular tachycardia utilizing the slow pathway for retrograde conduction and the fast pathway for anterograde conduction. **Panel A.** The ventricle was paced at a basic cycle length of 500 msec. The S_1-A_1 interval for the basic drive beat was 185 msec. At an S_1-S_2 interval of 470 msec, S_2 was conducted retrogradely to the atrium with an S_2-A_2 interval of 190 msec that resulted in an A_1-A_2 interval of 475 msec. A junctional escape beat followed. **Panel B.** At an S_1-S_2 interval of 460 msec, the S_2-A_2 interval (480 msec) was suddenly and markedly prolonged, resulting in an A_1-A_2 interval of 760 msec and suggesting failure in retrograde A-V nodal conduction through the fast pathway. Because at that time conduction occurred retrogradely through the slow pathway, the fast pathway was available for anterograde conduction, resulting in an unusual reversed form of reentrant tachycardia wherein the fast pathway was used for anterograde conduction (Ae-H intervals 135 to 145 msec) and the slow pathway for retrograde conduction (H-Ae intervals 340 to 350 msec). **Panel C.** At an S_1-S_2 interval of 260 msec, the retrograde His bundle deflection (H_2) emerged from the ventricular electrogram. Note that the H_2-A_2 interval was markedly prolonged (430 msec) and resulted in A-V nodal reentry in the form of ventricular echo. Note that tachycardia was not sustained due to block in the retrograde slow pathway. Abbreviations as in Figure 1. A* = dissociated atrial electrogram.

determined by the His-Purkinje system, and in the majority of patients the functional refractory period of the ventriculoatrial conducting system was shorter than that of the A-V conducting system, suggesting that the retrograde pathway had shorter refractoriness than the anterograde pathway (that is, the A-V node). Furthermore, ouabain did not appreciably affect retrograde refractoriness of the fast pathway.

The findings in group II, unlike those in group I, demonstrated that both the anterograde and retrograde limbs of the reentry circuit had electrophysiologic characteristics of the A-V node. The following findings support this contention: (1) conduction in the retrograde limb was longer than in group I patients, despite the fact that anterograde conduction was also longer in group II than in group I patients, and (2) in contrast to group I, ventriculoatrial conduction time in response to incremental ventricular pacing and the retrograde H_2-A_2 intervals in response to decreasing V_1-V_2 intervals increased after the administration of ouabain. The increases in H_2-A_2 intervals generally corresponded to the changes in H-Ae intervals and were relatively similar in magnitude to the changes observed in control subjects.

Refractoriness of the anterograde and retrograde limbs of the reentry circuit: It is generally believed that A-V nodal reentry represents functional dissociation of the A-V node into two separate pathways.[6–11] According to this theory, when anterograde block occurs in the fast conducting pathway with longer refractoriness, conduction occurs exclusively through the slow conducting pathway with shorter refractoriness. This theory is supported by the observation of discontinuous A-V nodal curves in some patients with paroxsymal supraventricular tachycardia.[8–11]

We were unable to demonstrate anterograde or retrograde discontinuous A-V nodal curves in any patient in group I. Furthermore, our observations suggest that in the majority of these patients, the retrograde fast pathway had shorter refractoriness than the anterograde slow pathway. In contrast, three of five patients in group II demonstrated anterograde discontinuous A-V nodal curves. In two of these three patients, the retrograde functional refractory period of the A-V node was longer than the anterograde functional refractory period of the A-V node, whereas in the third patient it was shorter. However, it should be pointed out that the retrograde effective refractory period of the A-V node was never attained in any patient in group I or in four of five patients in group II. The initiation of a reverse form of tachycardia in only one of these patients with utilization of the slow pathway for retrograde conduction at the time of failure in conduction in the retrograde fast pathway provides strong evidence for longer retrograde fast pathway effective refractoriness.[27] Ventriculoatrial block in this patient and the inability to reinitiate the tachycardia after the administration of ouabain suggest that the drug induced block in both pathways in the retrograde direction.

Role of A-V nodal bypass tracts: The findings in group I suggest that the retrograde limb of the reentry circuit is an extranodal pathway[28–31] that functions only in the retrograde direction. It is also possible that the retrograde limb is an intranodal pathway that connects to the His bundle, is insulated from the rest of the A-V nodal mass and has physiologic characteristics unlike that of the A-V node. Stronger evidence for one of these pathways will require morphologic and cellular studies in these patients. Because conduction in the retrograde limb of the reentry circuit and retrograde A-V nodal conduction in four of five patients in group II were shorter than conduction in the anterograde limb and never equalled or exceeded the latter, it may be argued that partial bypass of the A-V node with insertion of the proximal limb in the atrionodal region comprised the retrograde limb in these patients. However, this is unlikely because (1) conduction in the retrograde limb was relatively long, and (2) changes in H-Ae intervals corresponded to changes in H_2-A_2 intervals that were similar in magnitude to those observed in four of five control patients after the administration of ouabain.

The incidence of A-V nodal bypass tracts that function only in the retrograde direction in patients with paroxysmal supraventricular tachycardia is not known. In a study on the effects of verapamil in 13 patients with paroxysmal supraventricular tachycardia, Spurrell et al.[32] postulated the utilization of A-V nodal bypass tracts in 5 of 13 patients. However, systematic analysis of retrograde A-V nodal conduction and refractoriness and correlative observations on retrograde A-V nodal conduction and H-Ae intervals before and after the administration of verapamil were not available in their patients. Narula[33] suggested the presence of retrogradely functional A-V nodal bypass tracts in 8 of 19 patients with intact ventriculoatrial conduction and evidence of paroxysmal supraventricular tachycardia. However, the presence of Kent bundles functioning solely in the retrograde direction were not excluded in his study, nor were the characteristics of tachycardia assessed.

Clinical implications: Our findings indicate that the pathways in reentrant A-V nodal tachycardia may not be the same in all patients. Depending on the electrophysiologic properties of the anterograde and retrograde pathways, the inherent rate of tachycardia and the response to drugs will vary. Patients with retrograde A-V nodal bypass tracts or rapid retrograde conduction will have relatively faster rates, whereas patients who utilize the A-V node for both anterograde and retrograde conduction will have slower rates.

Digitalis has been advocated as the drug of choice if paroxysmal supraventricular tachycardia does not respond to usual vagotonic maneuvers. Our observations and those of others[10,12] suggest that digitalis is useful in the management of these patients because of the inability to sustain tachycardia and the decrease in rate of tachycardia and the echo zone after the administration of ouabain. Furthermore, our observations suggest that patients who utilize the A-V node in the reentrant process may benefit more from digitalis and drugs such as propanolol that induce delay in conduction or block in the anterograde or retrograde limb, or both.

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Quantitative Coronary Arteriography

Coronary Anatomy of Patients With Unstable Angina Pectoris Reexamined 1 Year After Optimal Medical Therapy

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The effect of optimal medical therapy on coronary arterial anatomy was evaluated in 25 patients with unstable angina pectoris. Coronary arterial diameter and the extent of stenosis were exactly quantified in two successive coronary angiograms performed in each patient at approximately a 1 year interval (range 4 to 31 months, average 12.4 months). The measuring device was a vernier caliper with an accuracy of 0.05 mm. After 1 year of medical treatment 69 stenoses of the three major coronary branches showed no significant change: The average degree of area obstruction of 27 stenoses of the right coronary artery was 79 and 84 percent in the initial and second studies, respectively; that of 26 stenoses of the left anterior descending artery 78 and 77 percent, respectively, and that of 16 stenoses of the left circumflex artery 73 and 83 percent, respectively. In 11 patients, 14 stenoses showed a distinct progression of more than 20 percent area obstruction. All six stenoses showing more than 90 percent obstruction in the first angiogram progressed to complete obstruction within 1 year. In five other patients area obstruction in five stenoses regressed by more than 20 percent. The anatomy of vessel segments distal to obstructions remained unchanged within 1 year. It is concluded from these quantitative measurements that the distribution and severity of coronary lesions are similar in patients with stable and unstable angina pectoris. Coronary anatomy showed no significant change after 1 year of medical treatment. The rate of progression was substantially lower than previously reported in patients with stable angina pectoris.

Unstable angina pectoris is a clinical syndrome of chest pain interposed between the syndromes of stable angina and myocardial infarction. From the patient's history a distinction is made between the three clinical manifestations. Unstable angina may be defined as (1) effort angina of recent onset (preceding 4 weeks), (2) effort angina with a recently changing pattern, that is, an increase in frequency or severity of ischemic cardiac pain, and (3) recent onset of angina at rest.

This variability in the clinical manifestation of unstable angina pectoris is associated with a broad spectrum of coronary artery disease as shown by angiography.[1,2] If only severe stenoses are considered, angiography reveals single vessel disease in approximately 30 percent of patients with unstable angina, double vessel disease in approximately 30 percent, triple vessel disease in approximately 30 percent and normal coronary arteries in the remaining 10 percent.

The variety of clinical manifestations and angiographically demonstrable anatomic patterns renders appropriate therapy difficult. In a large proportion of patients with unstable angina vigorous medical therapy relieves the acute attack and leads to a more stabilized anginal pattern.[3,4] However, this symptomatic improvement does not provide information about the influence of medical therapy on the underlying coronary arterial anatomy and, in particular, on the natural history of

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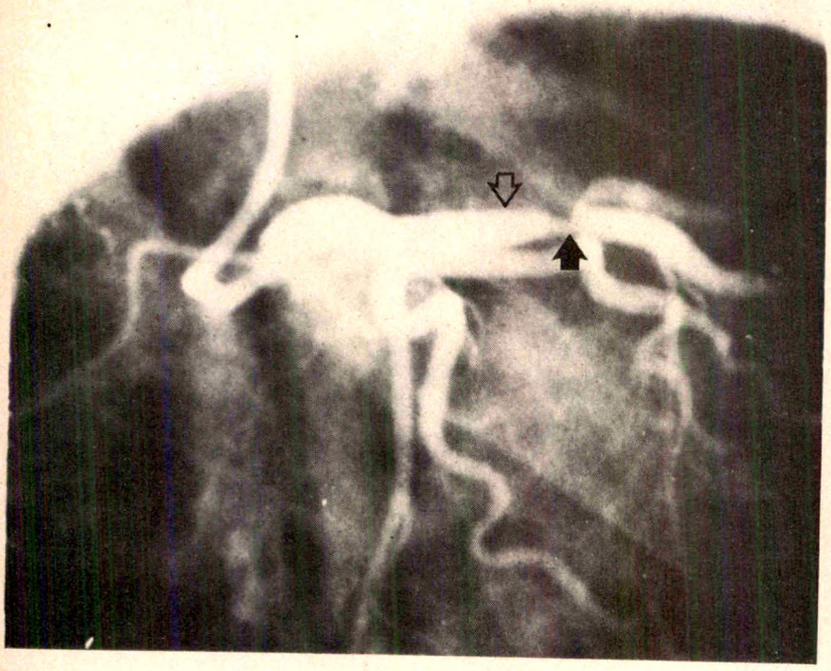


FIGURE 1. Coronary angiographic frame from a representative stenosis of the left anterior descending artery in the right anterior oblique projection. The **arrows** show the sites of measurements to calculate the degree of stenosis. **Open arrow** = prestenotic diameter (D_{norm}); **closed arrow** = stenotic diameter (D_{sten}). Note that the stenotic diameter is measured in at least four projections, and the degree of stenosis is then calculated by the formula percent area stenosis $= 1 - (D_{sten}^2/D_{norm}^2) \times 100$. In this formula D_{sten} is the calculated mean diameter from the measured diameters in the different projections. In this specific case the degree of stenosis was calculated as 84 percent of cross-sectional area.

the disease. In this study we reexamined the coronary arterial anatomy in 25 patients with unstable angina pectoris after approximately 1 year of optimal medical therapy. Coronary arterial diameter and the extent of stenosis were quantified exactly from the angiographic screen using a new measuring technique.

Methods

Patient Selection

The patients for this study were selected from the Alabama portion of a nationwide survey comparing medical and surgical treatment in patients with unstable angina pectoris.[5] The clinical diagnosis of unstable angina was made in all cases by a staff cardiologist. The criteria for this diagnosis were (1) a recent onset or a changing pattern of effort angina, and (2) a recent onset of angina at rest. The clinical situation must have been sufficiently severe to warrant admission to the coronary care unit. Transient electrocardiographic S-T or T wave changes, or both, during the ischemic attack were essential for inclusion in this study. Patients were admitted to the coronary care unit and initially treated with bed rest, isosorbide dinitrate and nitroglycerin sublingually. If they were taking propranolol the dose was usually maintained at 80 mg/day before coronary arteriography; otherwise, administration of the drug was not begun until after coronary arteriography. If a myocardial infarction was excluded by standard criteria after an observation period of 48 to 96 hours, informed consent was obtained, and selective coronary angiography (study A) and left ventricular angiography were performed.

Treatment groups: The result of the catheterization study was used to determine which group the patient entered: Group A, obligatory medical therapy; Group B, obligatory surgical therapy; or Group C, randomized to medical or surgical therapy. Patients were assigned to obligatory medical treatment (Group A) if they had normal coronary arteriograms, very mild coronary artery disease or very severe distal coronary artery disease or marked left ventricular dysfunction. Surgery was considered obligatory in the small group of patients who had an obstructive lesion of the left main coronary artery exceeding an estimated 50 percent of the diameter of the lumen. Other patients were randomly assigned to medical or surgical treatment.

Medical therapy included bed rest in the coronary care unit, administration of oxygen, propranolol, long-acting nitrates as often as every 2 to 3 hours, additional nitroglycerin as required, sedative drugs and, if necessary, digitalis and diuretic drugs and control of blood pressure. Anticoagulant therapy was used at the discretion of the physician. If this medical therapy failed, the patient was offered surgical therapy after 1 week. Otherwise the medically treated patients were followed up at average intervals of 3 months and had a second coronary angiogram (study B) at an average interval of 12.4 months (range 4 to 31 months).

Twenty-five patients were selected from the 55 patients randomized to medical therapy in the cooperative unstable angina protocol at this institution and were those patients consenting to repeat coronary angiography at the start of this investigation. No patients were lost to clinical follow-up during the interval covered by this study.

During the follow-up period medical therapy included vigorous treatment with propranolol to the point of control of symptoms or to a pulse rate of about 60/min, most frequently at a dose level of 160 mg/day; nitrates to the point of tolerance of headaches or to control angina; treatment of hypertension; strong encouragement of the patient to stop smoking; and instruction in a low-saturated fat diet. Medications were not used for lowering serum lipid levels. Antiplatelet agents were not prescribed.

Measurements

In the 25 medically treated patients comparable diameters of coronary arteries and the degrees of obstruction were measured in both the initial and the repeat angiogram with

a vernier device (accuracy 0.05 mm). Both 35 mm cinefilms and large film angiograms were available for each patient. Large films were used to identify exactly corresponding sites of measurements. Vessels without disease were measured exclusively on 35 mm films, whereas stenoses were evaluated using both cineangiograms and large films. For the projection of the 35 mm films a Tage-Arno projector was used. The enlargement factor of approximately 1:3 was determined exactly by measuring the catheter tip placed in the coronary ostium. Only the arteries coursing nearly parallel to the image plane were measured in the different projections; that is, we assessed the left anterior descending artery and the posterior descending branch of the right coronary artery in the right anterior oblique projection and the left circumflex artery and the main trunk of the right coronary artery in the left anterior oblique projection. To minimize errors from pin-cushion distortion, which can cause an error averaging 7 percent, the measurements were consistently performed near the central X-ray beam. Although we were unable to find any detectable change in luminal diameter during the cardiac cycle, we always measured at end-diastole to avoid a blurring effect from rapid heart movements or errors caused by axial or spatial rotations. This procedure is especially important in this comparative study.

Degree of stenosis: Taking into account the eccentric lumen of many obstructions, we measured atherosclerotic lesions in as many projections as possible including 35 mm cinefilms and large films. Sites of measurements in vessels with obstructions included the prestenotic segment, the narrowest portion of the obstruction, the immediate poststenotic segment and the peripheral segment of the vessel (Fig. 1). The degree of stenosis was calculated by the formula percent area stenosis = $1 - (D_{sten}^2/D_{norm}^2) \times 100$, where D_{norm} is the diameter of the undiseased prestenotic vessel and D_{sten} the average stenotic diameter calculated as the arithmetic mean determined from as many measurable diameters as possible. Each clearly defined stenosis was measured. In 58 stenotic vessels a total of 69 stenoses were measurable; in seven patients two stenoses and in two patients three stenoses were measurable in a single branch. Only in the three major branches—left anterior descending, left circumflex and right coronary artery—were a sufficient number of stenoses measurable to allow statistical analysis. The main stem of the right coronary artery was subdivided into a proximal, middle and distal third and the left anterior descending coronary artery into a proximal and distal segment with respect to the first septal perforator. In the left circumflex artery only stenoses between the origin of the vessel from the left main coronary artery and the most distal significant obtuse marginal branch were considered, and this section of the vessel was called the main stem of the left circumflex artery.

All angiograms were chosen at random and read by the same observer. To establish the precision of the measurements 25 stenoses in 14 angiograms were analyzed at two different times by the same observer in a pilot study. The differences in calculations of the degree of obstruction ranged from 0 to 11 percent (average difference 6.2 ± 3.0 percent [mean ± standard deviation]).

Validity of Method

The validity of this method in determining true vessel diameter particularly in obstructions has been tested in comparisons of intravital angiograms with postmortem histologic measurements of the same coronary lesions.[6] In 12 patients who had coronary angiograms and who died from various causes (average 3 months later), the coronary arteries were filled and fixed at autopsy under physiologic pressure using a modified Fulton technique.[7] Histologic sections were obtained and were measured using a scaled optical system. The procedure uses a magnification technique on the true section to allow more accurate planimetry of the coronary cross section. At 66 measuring points the diameter of coronary arteries measured from the intravital angiogram was compared with the vessel diameter found on postmortem histologic study. The plot demonstrated a clear linear relation between these two measurements, with a correlation coefficient of $r = 0.85$.

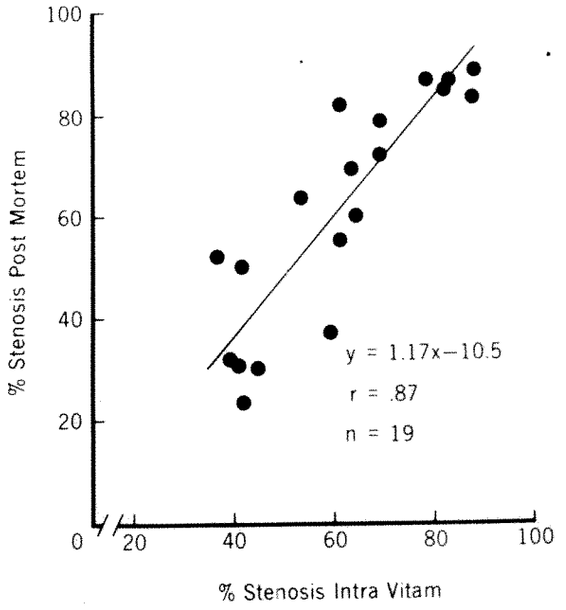


FIGURE 2. Correlation of percent stenosis measured intravitally (**abscissa**) and post mortem (**ordinate**) in nine hearts. n = number of comparable stenoses; r = correlation coefficient.

In 19 stenoses we measured prestenotic and stenotic diameters from the intravital angiogram in as many projections as possible. From these measurements we calculated the mean stenotic diameter, which then served as a reference for calculating the degree of stenosis. Subsequently we constructed a circle having the calculated mean stenotic diameter and compared the area ratio of the prestenotic and constructed stenotic circles with the area ratio measured post mortem. This relation yielded a correlation coefficient of $r = 0.87$ (Fig. 2).

Quantitative Measurements on Collateral Vessels

Because we found at least one severe stenosis bypassed with collateral vessels in 16 patients in this study, we attempted to assess the development of collateral vessels by quantification. In each patient who had a stenosis bypassed by collateral vessels the specific pathways[8] were evaluated in study A. Evidence for both anterograde and collateral filling or collateral filling alone was registered. With the vernier caliper the diameter of the vessel filled by collateral vessels and the diameter of the largest visible collateral vessel were measured. The density of collateral vessels was counted as visible vessels per 2 cm^2. These data were compared with the analogous data of study B. Only a distinct increase in at least two of the measured variables or the demonstration of a newly developed collateral pathway was considered progression in collateralization.

TABLE I

Angiographic Findings in 25 Patients With Unstable Angina Pectoris

Vessel	Patients (no.) 1 Vessel Disease	2 Vessel Disease	3 Vessel Disease
A. All Lesions			
RCA	1	...	...
+ LAD	...	5	...
+ LCf	...	2	...
+ LAD & LCf	...	...	13
LAD	...	...	...
+ LCf	...	4	...
Total	4%	44%	52%
B. Only Lesions With More Than 75 Percent Area Obstruction			
RCA	3	...	...
+ LAD	...	3	...
+ LCf	...	2	...
+ LAD & LCf	...	...	11
LAD	3	...	...
+ LCf	...	2	...
LCf	1	...	...
Total	28%	28%	44%

LAD = left anterior descending coronary artery; LCf = left circumflex coronary artery; RCA = right coronary artery

TABLE II

Average Degree of Stenosis (±1 standard error) Measured in the Initial (Study A) and Second (Study B) Coronary Angiograms

Vessel	Stenosis (no.)	Study A*	Study B*
RCA†			
Proximal	13	76 ± 7.3%	81 ± 5.1%
Middle	11	80 ± 9.1%	88 ± 5.1%
Distal	3	90 ± 5.7%	87 ± 7.0%
Mean	27	79 ± 5.1%	84 ± 3.3%
LAD‡			
Proximal	11	83 ± 3.4%	81 ± 3.4%
Distal	15	74 ± 6.9%	74 ± 6.2%
Mean	26	78 ± 4.2%	77 ± 3.8%
LCf			
Main stem	16	73 ± 8.1%	83 ± 4.4%

* There were no significant differences between values in studies A and B.

† The main stem of the right coronary artery is subdivided into a proximal, middle and distal third.

‡ The left anterior descending coronary artery is subdivided into a proximal and distal part with respect to the first septal perforator.

LAD = left anterior descending coronary artery; LCf = left circumflex coronary artery; RCA = right coronary artery.

Results

Distribution of patients with lesions: Table IA demonstrates the arteriographic distribution of all lesions in the first angiogram (study A) in the 25 patients studied. Patients with normal angiograms were not included because their treatment was not randomized. One patient (4 percent) had single vessel disease, in this instance a complete obstruction of the right coronary artery. Eleven patients (44 percent) showed double vessel disease in the first angiogram; the left anterior descending coronary artery was involved in nine patients. Thirteen patients (52 percent) had triple vessel disease.

In Table IB only stenoses of more than 75 percent area obstruction are considered. Of the 13 patients with triple vessel disease 2 (13 percent) had one minor stenosis in one vessel and therefore were reclassified as having double vessel disease. In contrast 6 (55 percent) of the patients with two vessel disease had only one severe stenosis and were reclassified in the group with single vessel disease.

Degree of stenosis: In the 25 patients all 69 stenoses of the three major coronary branches (2.8 stenoses/patient) were measurable and the data in studies A and B could be compared. Table II demonstrates the distribution of these 69 stenoses in the three branches—right, left anterior descending and left circumflex coronary artery—and shows the average degree of stenosis in the two studies. A total of 27 right coronary arterial stenoses demonstrated only a slight and insignificant mean increase in area obstruction from 79 to 84 percent. Twenty-six stenoses of the left anterior descending artery showed an even closer mean degree of narrowing (78 and 77 percent, respectively) in studies A and B. The overall increase of 16 left circumflex arterial stenoses from 73 to 83 percent was also not significant.

The insignificant changes in the average degree of stenosis suggests that the majority of patients had unchanged stenoses. The distribution of unchanged stenoses in the three major branches is shown in Table III. In 20 patients with stenoses of the right coronary artery, 15 (75 percent) had no change in obstruction from study A to study B. In 14 (64 percent) of 22 patients with

TABLE III

Number of Vessels Showing no Change in Degree of Stenosis Between the Initial (Study A) and Second (Study B) Coronary Angiograms and Their Collateral Blood Supply

Vessel	Stenosed Vessels Total no.	Vessels With No Change in Stenosis no.	%	Collateral Blood Supply None Visible in Study A	Unchanged in Study B	Increased in Study B
RCA	20	15	75	6	5	4
LAD	22	14	64	8	5	1
LCf	16	10	63	7	3	0

LAD = left anterior descending coronary artery; LCf = left circumflex coronary artery; RCA = right coronary artery.

TABLE IV

Vessels With Progression or Regression of Degree of Stenosis Between the Initial (Study A) and Second (Study B) Coronary Angiogram

Case no.	Vessel	Degree of Stenosis in Study (%) A	Degree of Stenosis in Study (%) B	Collateral Blood Supply
		Progression of Stenosis		
1	RCA	0	73	Progression
2	RCA	66/56/83	100	Only in study B
3	RCA	0	75	None visible
4	RCA	94	100	Only in study B
	LAD	91	100	Only in study B
5	LAD	93	100	Only in study B
6	LAD	81	83/44	None visible
7	LAD	49	78	None visible
	LCf	94	100	Only in study B
8	LAD	90	100	Only in study B
	LCf	91	100	Only in study B
9	LCf	72	91	None visible
10	LCf	0	81	None visible
11	LCf	68	99	Only in study B
		Regression of Stenosis		
12	RCA	80	49	Only in study A
13	LAD	82	44	None visible
14	LAD	88	65	None visible
15	LAD	88	69	None visible
16	LCf	70	49	None visible

LAD = left anterior descending coronary artery; LCf = left circumflex coronary artery; RCA = right coronary artery.

stenoses of the left anterior descending artery and in 10 (63 percent) of 16 patients with stenoses of the left circumflex artery in study A there was no change in the degree of stenosis between studies.

Progressive and regressive stenoses: Stenoses that showed a distinct (more than 20 percent) change over the 1 year interval are of special interest. Fourteen of 69 stenoses (20 percent) demonstrated a marked increase in area obstruction (Table IV). All six stenoses of 90 percent or more in study A progressed to complete obstruction in the repeat angiogram. In addition, Patient 2, who had three right coronary arterial stenoses in study A, had complete occlusion of this vessel in study B. Three vessels (two right coronary arteries, one left circumflex artery) that had no disease in the first study manifested a significant stenosis in study B. Three patients had a measurable progression of disease in two vessels. In two of these patients complete obstruction developed in two vessels each.

In contrast, a distinct regression (more than 20 percent) in the severity of stenosis was found in five other patients (Table IV, Fig. 3). Only one of these patients (Case 12) had a hyperlipidemia (type IV) that was successfully treated with diet in the follow-up study.

Collateral vessels: The distribution and development of collateral vessels are shown in Tables III to V. Quantitative evaluation of collateral vessels was possible in 16 patients (64 percent), 12 with collateralization of one stenotic vessel and 4 with collateralization of two obstructed vessels. Of the 20 obstructed vessels 11 were right, 6 left anterior descending and 3 left circumflex coronary arteries. Thus, 55 percent of obstructed right coronary arteries were collateralized compared with only 27 percent of obstructed left anterior descending

TABLE V

Collateralization in the Initial (Study A) and Second (Study B) Coronary Angiograms

Vessel	Obstructed Vessels (no.) in Study A: Total	With 100% Obstruction	With Collateral Vessels	Vessels (no.) in Study B With Quantitative Increase in Collateralization
RCA	20	8	11	7
LAD	22	4	6	4
LCf	16	3	3	3
Total	58	15	20	14

LAD = left anterior descending coronary artery; LCf = left circumflex coronary artery; RCA = right coronary artery.

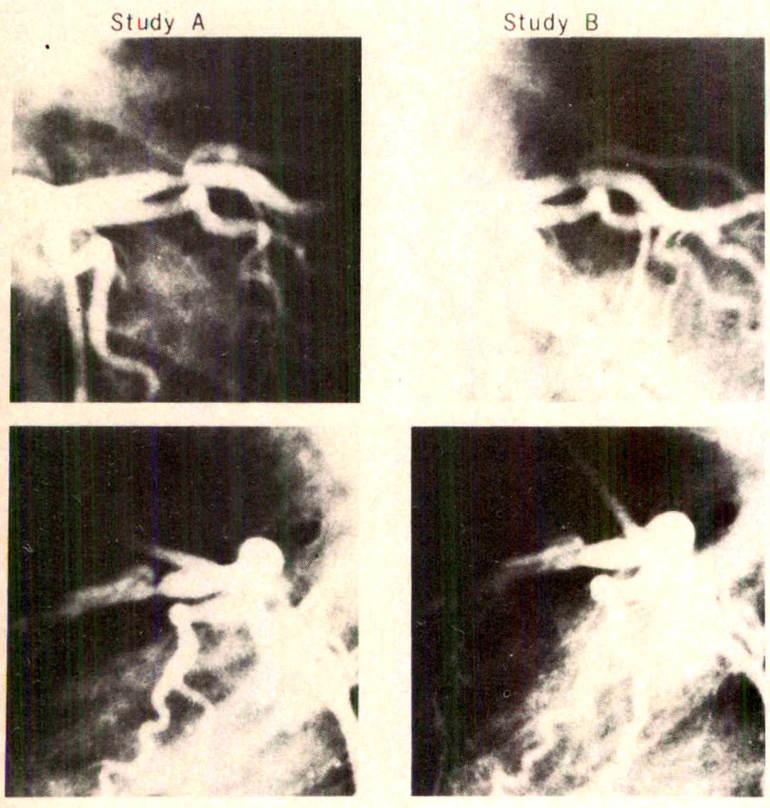


FIGURE 3. Patient 15 (Table IVB). Angiographic demonstration of a regressive stenosis in the left anterior descending artery in the right anterior oblique projection (**top**) and lateral projection (**bottom**). In the initial study (**left**) the degree of obstruction is 88 percent; in the repeat study 13 months later (**right**), it is 69 percent.

and 19 percent of obstructed left circumflex arteries. The average degree of stenosis in vessels with resultant collateral circulation was 95 percent, but in 75 percent of the collateralized vessels a complete obstruction was present. All vessels with complete obstruction in study A showed collateralization, compared with only 21 percent of vessels with obstructions of 75 percent and none of those with stenoses of less than 75 percent area obstruction. In study B only 14 vessels (that is, 24 percent of all obstructed vessels) demonstrated a measurable increase in collateralization over that in study A. Seven of these stenoses progressed from high degree to complete obstruction between studies (Table IV). However, it should be emphasized that 38 (66 percent of all obstructed vessels) did not have visible collateralization in study A.

Discussion

In 1971 Fowler[9] first used the now widely accepted term "unstable angina" for a spectrum of clinical symptoms in ischemic heart disease. The patients affected by this type of suddenly worsening angina were considered to be at high risk of myocardial infarction and sudden death in the near future.[10,11] Surgical therapy was suggested[12,13] to prevent this unfavorable outcome; however, some randomized trials[14,15] of medical and surgical treatment of unstable angina have recently shown encouraging results from medical therapy when the acute stage is controlled.

The natural history of medically treated patients with unstable angina pectoris is not known with precision and depends largely on the underlying coronary artery disease. The present method of evaluating coronary arterial findings is subjective and is not ideal for precise comparison of angiograms in the same patient. We know from several studies[17–19] that the subjective element in detecting and grading coronary stenoses leads to a wide range of intra- and interobserver variability. However, truly objective, reproducible measurements would allow an adequate comparison between angiograms. Since Gensini et al.[20] began to measure coronary diameters before and after administration of nitroglycerin, several techniques have been developed to make these measurements more reliable and easier to perform.[21,22] The results obtained with our own technique are in close agreement with the ones obtained with highly elaborate methods.[20,23]

Distribution of lesions: Plotnick and Conti[16] proposed that only patients with operable coronary lesions be included in a prospective randomized trial of therapy for coronary artery disease. We excluded from our study patients with unstable angina and normal coronary arteries at angiography and treated them medically. Slightly more than half of our patients (13 of 25) had triple vessel disease. Of the 11 patients with double vessel disease the majority had left anterior descending

artery disease. This distribution is similar to the data published by Hultgren.[24]

When only vessel obstructions of more than 75 percent (cross-sectional area) are considered, the distribution in our series was quite consistent with previously published data. In a review of eight series of patients with angiographic studies including 408 patients with unstable angina, Day et al.[4] calculated that 25 percent of patients had single, 34 percent double and 41 percent triple vessel disease. This distribution is similar to that reported for groups of patients with stable angina.[25] The similar extent of coronary disease in the patients with stable and unstable angina supports the concept that the difference in clinical symptoms is not due to demonstrable differences in coronary arteriographic anatomy. Features other than angiographically demonstrable factors are crucial for the clinical course.

Degree of obstruction: The average degree of obstruction in the three major coronary branches of our patients is one that is widely accepted as "critical" in causing reduction in coronary blood flow. From experimental data[26] it is known that at least three fourths of the cross-sectional area of a vessel must be occluded to create insufficient myocardial perfusion even at rest. Our values are in this range of stenosis for every branch, if one considers the subdivision of the right coronary artery into a proximal, middle and distal segment and the left anterior descending artery into a proximal and distal segment with respect to the first septal perforator. Because most investigators evaluate the coronary angiogram on a more subjective basis, there are few reported quantitative data about coronary morphometry in a clinically defined group of patients with coronary heart disease. In our own previous studies using the same technique of measurement,[27] we found the degree of stenosis in the left anterior descending and left circumflex arteries is very similar to that in patients with stable angina. However, we found that patients with stable angina have significantly less obstruction in the right coronary artery than patients with unstable angina. The reason for this finding remains speculative.

In the present investigation we found no significant difference between the first and second angiographic study in the degree of obstruction in any of the vessels under scrutiny. In their angiographic study of 73 patients with stable angina pectoris Bemis et al.[28] observed pronounced progression of coronary stenosis in the 1st year after the initial angiogram. In addition, they found the most striking progression at the site of previous lesions. If there is a difference in the pace of progression of coronary artery disease between patients with stable and unstable angina pectoris one might expect a faster deterioration in the latter group. However, our data do not confirm this theory. It seems unlikely that the rapid progression of an already severe stenosis is responsible for the changing clinical symptoms of unstable angina pectoris. In our patients with unstable angina pectoris the coronary lesions most frequently remained unchanged in the 1st year after onset of the syndrome and did not show a continued progression of obstruction. The anatomic lesions underlying the clinical findings of unstable angina remained identical in most patients receiving optimal medical therapy when their symptoms were stabilized. This finding again suggests that the troublesome clinical instability may be due more to a time-limited dynamic imbalance between myocardial blood supply and demand than to an accelerated progression of an already high degree of obstruction. In this range of severe stenosis minimal increases in obstruction or in demand for blood would result in a critical decrease in coronary pressure and flow with resultant symptoms.[29]

Progressive stenoses: The 14 stenoses that progressed in degree of obstruction between study A and study B were nearly equally distributed in the three major branches. The percent of stenoses that showed progression in our study (20 percent of lesions) was relatively low in comparison with the 52 to 76 percent range reported in follow-up studies of patients with stable angina.[28,30–32] It is unlikely that the unstable clinical course at the time of the first angiogram in our patients was the deciding factor in our small percent of stenoses showing progression. On the contrary, one might have expected a greater degree of progression of obstruction in our patients with unstable angina.

Three patients (4 percent) had a rapid development of severe stenoses at sites that were normal in the initial angiogram. This relatively low rate of progression in comparison with that reported by others[28] also supports the concept of an imbalance between myocardial oxygen need and supply at the onset of the unstable anginal syndrome.

Half of the vessels with progressive stenosis had an initially high degree of obstruction (90 percent or more) or multiple stenotic lesions and later had complete obstruction. All three major branches were equally involved with this phenomenon. Five subtotal stenoses that progressed to total occlusion were found in three patients who showed progressive obstruction in two major vessels. Except in one patient (Case 5) the occlusion of a vessel after the initial angiogram resulted in a myocardial infarction in the area supplied by the occluding vessel.

Regressive stenoses: The reversibility of atheromatous disease has been studied extensively in experimental animals.[33] In primates the regression of coronary atherosclerosis induced by a hypercholesterolemic diet has been demonstrated. In man malnutrition and wasting diseases have been associated with an apparent decrease in atherosclerotic plaques. To our knowledge there are few angiographic data supporting the concept of regressing coronary lesions.[34] Most investigations do not mention the possibility of regression, and Bemis et al.[28] expressly denied that it occurred in their study. The amount of measured regression seen in our study was not limited by the degree of accuracy of our method. In an average size coronary vessel of 2.0 mm diameter a 20 to 30 percent difference amounts to 0.4 to 0.6 mm, whereas our measuring device can detect differences as small as approximately 0.05 mm. Stenoses are carefully examined in as many projections as possible. We are aware of the difficulties in assessing re-

gression of disease under the limitations of coronary angiography, but perhaps such a careful quantitative evaluation of coronary angiograms opens new possibilities in assessing in man this well described phenomenon in animals.

Collateral vessels: In our study the percent of vessels showing collateralization of severe obstructions was lower than in the study of Fischl et al.[1] In patients with stable angina pectoris the incidence of collateralization is reported to be significantly greater.[35,36] As Fischl et al.[1] suggested, this could be one reason for the increased vulnerability of the myocardium to even minor changes in degree of stenosis or myocardial oxygen demand in patients with unstable angina. In our study most of the vessels with severe stenoses (38 vessels or 66 percent) did not show any angiographically visible collateralization. Only 14 stenosed vessels (24 percent) demonstrated a progression in collateral blood supply: 64 percent of these also had a distinct progression in the degree of stenosis. All vessels with complete obstruction in the initial study showed collateralization, whereas only 21 percent of the vessels with 75 percent or more obstruction (but less than 100 percent) exhibited collateralization and none of the vessels with stenoses of less than 75 percent obstruction manifested collateral circulation.

The paucity of collateral vessels in our group of patients, together with the insignificant increase in collateral blood supply between studies, again supports the theory that unstable anginal symptoms may reflect a temporary myocardial underperfusion rather than a lasting change in flow pattern. Although the factors precipitating the syndrome of unstable angina are often not clear, our findings suggest that the syndrome is probably not due to a demonstrable rapid worsening of coronary artery disease evoking increased collateral channels to ischemic myocardium.

Clinical features: Evaluation of the clinical records did not reveal any significant correlation between any of our patient groups—that is, patients with no change or progressive or regressive disease over the interval—and hypertension and smoking behavior. Actually, two of the five patients with regressive disease continued to smoke at least 1 pack of cigarettes a day. Unfortunately, serum lipid levels were not checked routinely during the first admission, but the serum lipid levels during the follow-up examinations could not be correlated with angiographic findings in any of our patient groups.

Conclusions

Although it is difficult to determine all the factors that may contribute to the sudden deterioration of myocardial blood supply, coronary angiography, particularly when repeated, may be helpful in outlining some of the important factors. Careful quantitative examination is necessary to establish exact comparative studies. The data from our study show strong evidence that in most of these patients with unstable angina pectoris there is an insignificant amount of progression in coronary arterial narrowing over a 1 year period. Thus, only 14 of 69 stenoses (20 percent) demonstrated a marked increase in degree of obstruction. However, six of these progressing stenoses were of 90 percent severity in the initial study and did progress to complete obstruction during the interval. This supports the theory that unstable angina pectoris may be the clinical manifestation of a temporary period during the course of coronary artery disease in which a dynamic imbalance exists between myocardial blood supply and blood demand and leads to the profound clinical instability:

1. In general, the distribution and severity of lesions in these patients indicate that the coronary arterial anatomy is not significantly different in stable and unstable angina pectoris[27] but a variation in severity of clinical symptoms may develop in certain patients for causes that are, as yet, unknown.
2. The rate of deterioration of coronary lesions was slower in our group of patients than the rate reported in more qualitative studies of patients with stable angina pectoris.
3. The paucity of collateral vessels found initially in our patients suggests the concept of the appearance of transient myocardial ischemia. If a sudden increase of the degree of stenosis had led to the clinical picture of unstable angina, one would have expected a substantial increase of collateral vessels in the interval between angiograms. But only one fourth of all stenotic vessels demonstrated a significant increase in angiographically measurable collateral channels. Most of these vessels manifested in the initial angiogram subtotal stenoses that progressed to complete occlusion.
4. Stenoses of 90 percent or greater area obstruction were the lesions that most frequently progressed to complete occlusion during the interval of 4 to 31 months (average 12.4 months) between coronary angiograms in this investigation.
5. In these high quality coronary angiograms, we demonstrated regression of coronary arterial stenoses in a few patients.

Sequential angiography during and after the acute stage of unstable angina contributes anatomic pathologic data indicating that unstable angina pectoris is not the manifestation of a specific coronary lesion or lesions but a phase of the spectrum of possible clinical events that can occur during the course of atherosclerotic heart disease.

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Exercise-Induced Increase in Diastolic Pressure: Indicator of Severe Coronary Artery Disease

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The diastolic blood pressure response to treadmill exercise testing was analyzed in 281 patients. Diastolic blood pressure was measured at rest, during each stage of exercise, immediately on recovery, and 1, 3 and 5 minutes into the recovery period. No change or a decrease in diastolic blood pressure was considered a normal response. An increase in diastolic blood pressure of more than 15 mm Hg on at least two determinations, comparing values at rest with those on exercise, was considered an abnormal response. Only patients showing a normal increase in systolic blood pressure during exercise were included. Two hundred and nine patients had a normal and 72 patients an abnormal diastolic blood pressure response. In a subgroup of 41 patients who underwent coronary arteriography, 50 percent of patients with a normal diastolic pressure response had normal coronary arteries, compared with 17 percent of those with an abnormal response ($P < 0.03$). Only 11 percent of patients with a normal diastolic pressure response had triple vessel or left main coronary artery disease, compared with 44 percent of patients with an abnormal response ($P < 0.03$). Blood pressure at rest (132/84 mm Hg) and peak heart rate (mean 155 beats/min) were similar in each group. There was no significant difference between exercise-induced ischemic S-T segment changes in the two groups (13 percent for patients with a normal diastolic pressure response versus 15 percent for those with an abnormal diastolic pressure response). In conclusion, an abnormal diastolic pressure response to treadmill testing may be a good indicator of coronary artery disease even in the absence of S-T segment changes.

The response of systolic blood pressure to maximal treadmill exercise testing has useful diagnostic and prognostic implications. A failure to increase systolic pressure during exercise, or exercise-induced hypotension, correlates with an increased prevalence of severe two or three vessel coronary artery disease[1–4] and with a reduced ejection fraction at rest. In addition, patients with the lowest systolic pressure response to exercise are at greatest risk for subsequent death due to coronary heart disease.[1,3]

The normal diastolic blood pressure response to exercise is no change or a slight decrease (less than 10 mm Hg) during submaximal or maximal exercise and a small decrease during the recovery phase (less than 4 mm Hg).[5–7] The present study describes diastolic blood pressure responses recorded in a group of symptomatic patients referred for treadmill testing. Patients with an abnormal response, defined as greater than 15 mm Hg elevation in diastolic blood pressure, had a greater prevalence and severity of coronary artery disease than those with a normal response, independent of the presence or absence of ischemic changes in the exercise electrocardiogram.

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Material and Methods

Patients: The study population included all patients referred for exercise testing over a 2 year period. Patients were referred for evaluation of symptoms, usually chest pain. Two hundred eighty-one exercise records were classified as normal or abnormal on the basis of diastolic blood pressure response. A normal response was defined as no change or a decrease in diastolic pressure associated with increasing systolic pressure. An abnormal response was defined as an increase of more than 15 mm Hg in diastolic pressure; this response was selected because a change of this magnitude is easy to detect during exercise. Two determinations demonstrating a 15 mm Hg increase were required to increase the reliability of the measurements recorded during exercise. Only patients who demonstrated a normal increase in systolic blood pressure during exercise were included for analysis, in order to avoid an influence of inappropriate systolic blood pressure responses on diastolic changes.

Historical data, including a history of hypertension and chest pain, and exercise electrocardiographic and hemodynamic data were tabulated for each patient. A subgroup of 41 patients who underwent cardiac catheterization and coronary angiography within 1 month of the exercise test were analyzed for the presence and severity of coronary artery disease. Single vessel stenosis of less than 75 percent was used as the criterion for excluding coronary heart disease. Greater degrees of stenosis or distribution, or both, were tabulated with clinical and electrocardiographic data.

Exercise protocol: After informed consent was obtained, control electrocardiograms and blood pressure determinations were obtained with the patients seated. Rhythm strips were then obtained with the patients standing and after 45 seconds of hyperventilation. Submaximal (85 percent of maximal rate) treadmill testing was performed utilizing the Bruce protocol.[8] The electrocardiogram was monitored continuously with an oscilloscope, and blood pressures and electrocardiographic rhythm strips were obtained at 2 minutes into each stage of the protocol, at peak exercise and 1, 3 and 5 minutes into the recovery period. A bipolar (CB_5) precordial lead was used, with calibration before each test. Diastolic blood pressure was measured at phase V (disappearance of sounds). The average of at least two separate exercise determinations, or exercise and immediate recovery determinations, was used in calculating the change in diastolic pressure from baseline. Diastolic pressure could not be accurately determined in 35 patients and these cases were excluded.

Results

Exercise data: In 72 of the 281 patients the response was classified as abnormal (increase in diastolic blood pressure greater than 15 mm Hg), and in 209 patients the response was normal (no change or decrease in diastolic pressure). The ages and resting blood pressures were not significantly different in any group (Table I). A history of hypertension was equally prevalent in each group (29 percent for both normal and abnormal responses). Thus, abnormal diastolic pressure responses to exercise cannot be explained by factors relating to the presence of a history of systolic or diastolic hypertension at rest. In fact, mean resting diastolic blood pressure was actually lower in the abnormal than in the normal responders (73 versus 84 mm Hg).

The change in systolic pressure was equal in the two groups and comparable with previously reported normal responses.[1] Abnormal diastolic pressure responses therefore did not relate to abnormalities in the systolic

TABLE I

Characteristics of Patients With Normal and Abnormal Diastolic Blood Pressure Responses to Exercise (mean ± standard deviation)

	Abnormal Response* (no. = 72)	Normal Response* (no. = 209)
Age (yr)	48 ± 12	45 ± 13
Resting blood pressure (mm Hg)	126 ± 17/ 73 ± 11	132 ± 18/ 84 ± 11
Δ Systolic pressure (mm Hg)	50 ± 25	55 ± 25
Δ Diastolic pressure (mm Hg)	+24 ± 5	−5.6 ± 5
Peak heart rate (beats/min)	155 ± 25	155 ± 26
FAI (%)	29 ± 17	27 ± 18
MI on ECG (no.)	22 (31%)	32 (15%)†
Chest pain (%)	69	63
Hypertension by history (no.)‡	21 (29%)	61 (29%)

* Abnormal = exercise-induced increase in diastolic blood pressure greater than 15 mm Hg; normal = no change or decrease in diastolic blood pressure.

† $P < 0.01$.

‡ Hypertension = history of elevated blood pressure at rest requiring medical treatment.

FAI = functional aerobic impairment; MI on ECG = pattern of transmural myocardial infarction in the electrocardiogram at rest.

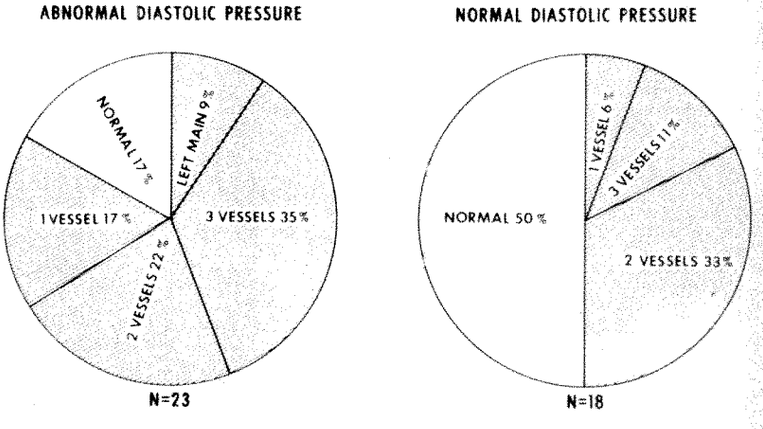


FIGURE 1. Prevalence of coronary artery disease in 41 patients who underwent coronary angiography and exercise testing within 1 month. The **shaded portions** represent patients with coronary artery disease (greater than 75 percent stenosis of at least one major vessel) on coronary angiography. Abnormal diastolic pressure is defined as an exercise-induced increase in diastolic blood pressure of more than 15 mm Hg; normal diastolic pressure indicates no change or a reduction in diastolic pressure. N = number of patients.

TABLE II

Hemodynamic and Angiographic Data in 41 Patients With Cardiac Catheterization (mean ± standard deviation)

	Age (yr)	Peak HR	Blood Pressure at Rest	CI	EF (%)	Segmental Contraction Abnormalities
Normal responders* (no. = 18)	49 ± 9	139 ± 26	133 ± 16/ 87 ± 11	2.8 ± 0.62	51 ± 14	6 patients (33%)
Abnormal responders* (no. = 23)	51 ± 10	144 ± 22	132 ± 16/ 77 ± 9	2.8 ± 0.42	51 ± 12	17 patients (74%)†

* Abnormal responders = patients with an exercise-induced increase in diastolic blood pressure greater than 15 mm Hg; Normal responders = patients with no change or a decrease in diastolic blood pressure.
† $P < 0.03$.
CI = cardiac index (liters/min per m^2); EF = ejection fraction (%); HR = heart rate (beats/min).

blood pressure response to exercise. Peak heart rate was similar in each group (mean 155 beats/min), reaching 85 percent of the predicted maximum for age. A similar percent of patients in each group gave a history of chest pain, typical or atypical of angina pectoris, and a similar percent (11 to 15 percent) had positive electrocardiographic signs of ischemia (greater than 1 mm horizontal or downsloping S-T depression 0.08 second after the S wave).

Hemodynamic and angiographic data: Forty-one patients underwent cardiac catheterization within 1 month of exercise testing, 18 with a normal and 23 with an abnormal diastolic blood pressure response. The results are summarized in Figure 1. Fifty percent (9 of 18) of the patients who had a normal diastolic blood pressure response had normal coronary arteries, and 11 percent (2 of 18) had triple vessel disease. None had disease of the left main coronary artery. In contrast, only 17 percent (4 of 23) of patients with an abnormal diastolic blood pressure response had normal coronary arteries, whereas 35 percent (8 of 23) had triple vessel disease and 9 percent (2 of 23) had disease of the left main coronary artery. The differences in percent of patients in each group with normal coronary arteries and triple vessel or left main coronary artery disease are statistically significant ($P < 0.03$).

Other hemodynamic and angiographic data obtained at cardiac catheterization are shown in Table II. The mean age and peak exercise heart rate were similar. Mean cardiac index was the same for both groups (2.8 liters/min per m^2), as was left ventricular ejection fraction (51 percent). However, 74 percent of the patients with an abnormal diastolic blood pressure response had segmental contraction abnormalities on left ventriculography compared with only 33 percent of those with a normal response ($P < 0.05$). Thus, it appears that an abnormal diastolic blood pressure response to treadmill exercise is associated with a greater prevalence of coronary artery disease, a greater severity of disease and a greater frequency of left ventricular contraction abnormality on cardiac catheterization. The sensitivity, specificity and predictive value of abnormal diastolic pressure response were calculated on the basis of the data shown in Figure 1.[9] The sensitivity was 68 percent, specificity 69 percent and predictive value 83 percent.

To determine whether the patients who underwent cardiac catheterization are representative of the entire group studied, various clinical and hemodynamic variables were compared in the subgroups who did and did not undergo this procedure. Table III shows various characteristics of the normal population. Among patients with a normal diastolic blood pressure response, those who underwent cardiac catheterization had a slightly greater incidence rate of classic angina (50 versus 37 percent), ischemic changes on exercise testing (17 versus 13 percent) and a pattern of myocardial infarction in the resting electrocardiogram (39 versus 15 percent), but the differences were not statistically significant. These factors may have influenced the decision to perform cardiac catheterization. Age, blood pressure at rest and degree of change in diastolic blood pressure during exercise were not different in the total normal group and those who underwent catheterization.

Table IV shows the same characteristics in the group with an abnormal diastolic blood pressure response.

TABLE III

Features of Patients With a Normal Diastolic Blood Pressure Response*

	Entire Group (no. = 209)	Patients With Cath (no. = 18)
Age (yr)	45 ± 13	49 ± 9
% Female	38	44
Hypertension (%)	29	17
MI on ECG (%)	15	39
Angina: typical/atypical (%)	37/26	50/28
Peak heart rate (beats/min)	155	138
Positive ischemic response (%)†	13	17
Blood pressure at rest (mm Hg)	132/84	130/81
Δ Diastolic blood pressure (mm Hg)	−5.6	−4.5

* Normal = no change or a decrease in diastolic blood pressure with exercise.
† Greater than 1 mm horizontal or downsloping S-T segment depression 0.08 second after the S wave.
Cath = cardiac catheterization; MI on ECG = pattern of transmural myocardial infarction in the electrocardiogram at rest.

TABLE IV

Features of Patients With an Abnormal Diastolic Blood Pressure Response*

	Entire Group (no. = 72)	Patients With Cath (no. = 23)
Age (yr)	48 ± 12	51 ± 00
% Female	43	17
Hypertension (%)	29	26
MI on ECG (%)	31	20
Angina: typical/atypical (%)	40/29	50/17
Peak heart rate (beats/min)	155 ± 25	154 ± 22
Positive ischemic response† (%)	15	30
Blood pressure at rest (mm Hg)	126/73	129/74
Δ Diastolic blood pressure (mm Hg)	↑24	↑24

* Abnormal = an exercise-induced increase in diastolic blood pressure greater than 15 mm Hg.
† Greater than 1 mm horizontal or downsloping S-T segment depression 0.08 second after the S wave.
Cath = cardiac catheterization; MI on ECG = pattern of transmural myocardial infarction in the resting electrocardiogram.

As in the normal population, the abnormal responders who underwent cardiac catheterization had a greater incidence rate of classical angina (50 versus 40 percent) and ischemic electrocardiographic changes on exercise testing (30 versus 15 percent). A pattern of myocardial infarction in the resting electrocardiogram was less common in the group with cardiac catheterization than in the total group of abnormal responders (20 versus 31 percent). Age, blood pressure at rest and degree of change in diastolic blood pressure during exercise were equivalent in the total group with an abnormal blood pressure response and in those who had cardiac catheterization. These comparisons suggest that the subgroups of abnormal and normal responders who underwent cardiac catheterization are representative of the larger populations.

Discussion

Abnormal diastolic blood pressure response as an index of coronary artery disease: Our data demonstrate that exercise-induced elevation of diastolic blood pressure identifies a population having a high frequency and degree of severity of coronary artery disease.[10] These findings are independent of ischemic electrocardiographic changes induced by exercise because 13 percent of the group with a normal diastolic blood pressure response had a positive ischemic response in the electrocardiogram, whereas 15 percent of the group with an abnormal diastolic response had a positive ischemic response. The design of our study purposely excluded patients with an abnormal systolic blood pressure response to exercise; therefore, abnormal diastolic pressure responses are not related to systolic blood pressure abnormalities. Sensitivity, specificity and predictive value figures of 68, 69 and 83%, respectively, indicate that abnormal elevation of diastolic blood pressure has the potential to act as an indicator of coronary artery disease.

Some investigators have questioned the reliability of diastolic blood pressure measurements taken during exercise.[1] We avoided this problem by requiring at least two determinations to demonstrate a change. Because this was a retrospective study, it is unlikely that observer bias influenced the recording of the blood pressure. The fifth Korotkoff sound (disappearance of sound) was chosen because it could be more reliably determined than the fourth (muffling of sound) with the background noise of the treadmill. However, there were 35 patients in whom this point could not be accurately determined and these patients were excluded.

Mechanism of increase in diastolic blood pressure as a response to exercise: This mechanism is unknown. It has been suggested that there is a muscle afferent feedback mechanism whereby, when muscle contraction occurs, afferent signals are sent from receptors in exercising muscle to the brain[11–15] stimulating sympathetic centers. Coote et al.[12] demonstrated a greater increase in mean arterial pressure when the muscle is rendered ischemic than when ischemia is absent. There is evidence that this reflex exists in man.[15–18] McCloskey and Mitchell[14] showed that the reflex is most likely excited through a metabolic mechanism. Inadequate cardiac output relative to local tissue demands generating ischemia would, therefore, affect blood pressure responses to exercise. Bruce et al.[19] previously showed that men with coronary heart disease have a higher peripheral resistance and a lower cardiac output and systemic pressure during exercise than healthy men.

It is known that patients with congestive heart failure have an increased vascular sodium content, which tends to limit vasodilation. This is thought to be a protective mechanism to maintain blood pressure during exercise[20] because patients with congestive heart failure have suboptimal increases in cardiac output and local muscle blood flow with exercise.

If the local metabolic feedback mechanism is operative in our patients, it is probably generated initially by inadequate cardiac output relative to the needs of the exercising muscles creating local tissue ischemia and setting the stage for reflex increases in blood pressure. If our patients had subclinical heart failure there may have been an added influence of inability of the local resistance vessels to dilate normally because of an increased intravascular sodium content. The result would be a failure of local metabolic vasodilatory mechanisms to override the central sympathetic responses to exercise, causing arteriolar constriction and elevation of diastolic blood pressure. It is reasonable to hypothesize suboptimal increases in cardiac output during exercise in our group with an abnormal diastolic blood pressure response because 83 percent of this group had coronary artery disease and 74 percent had left ventricular contraction abnormalities at rest.

Regardless of mechanism, we have found that an exercise-induced increase in diastolic blood pressure (more than 15 mm Hg over the baseline value) is a useful finding. It identifies a group of patients with a high prevalence of coronary artery disease of an advanced degree whether or not there are coexisting electrocardiographic changes.

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Abnormal Electrocardiographic Responses to Exercise in Patients Referred for Noninvasive Evaluation of Occlusive Peripheral Arterial Disease

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Fifty consecutive patients were referred to the noninvasive laboratory for evaluation of suspected peripheral vascular disease. There were 30 men and 20 women aged 27 to 88 years (mean 63). Measurement of cardiovascular risk factors revealed the following distributions: cigarette smoking 90 percent, hypertension 28 percent, diabetes mellitus 22 percent and hyperlipidemia 6 percent. Eight patients had a history of angina pectoris, 7 a prior myocardial infarction, 5 a cerebrovascular accident and 11 prior peripheral arterial revascularization surgery. Evaluation detected 32 patients (64 percent) with occlusive arterial disease of the lower limbs. Lead II of the electrocardiogram was monitored during and 1, 2, 3, 4, and 5 minutes after treadmill exercise with a limiting grade of 10 percent at 2.5 miles/hour. The mean resting and maximal heart rates for the study group were, respectively, 78 and 106 beats/min. The average treadmill speed attained was 1.9 miles/hour at a mean duration of 3.8 minutes. Thirty-seven subjects (74 percent) had normal electrocardiographic responses to exercise. Of 13 patients (26 percent) with an abnormal exercise electrocardiogram, 7 had possible ischemic S-T segment responses. Six subjects manifested frequent premature ventricular complexes during exercise. Four other patients had abnormal S-T segments in the resting electrocardiogram (two had a pattern of left bundle branch block, and two a pattern of left ventricular hypertrophy and strain).

A survey of 60 peripheral vascular laboratories in the United States revealed that only 29 percent of the responding 34 centers routinely performed electrocardiographic monitoring during exercise testing. It is concluded that (1) electrocardiographic monitoring during exercise in the peripheral vascular laboratory can provide useful information regarding S-T segment responses, (2) abnormal S-T segment responses in patients with suspected peripheral vascular disease are frequently manifested at low levels of work load, and (3) such routine monitoring should be performed for patient safety.

It is generally recognized that the most common and important form of occlusive peripheral arterial disease is arteriosclerosis obliterans,[1] and the frequent association of atherosclerotic involvement of the lower limbs and coronary artery disease has been well established. In light of the large incidence of cerebrovascular disease as well as aortic involvement in patients with coronary artery disease, there should be little doubt that the association of coronary artery and peripheral vascular disease occurs because the same pathologic process is involved in each.[1–5]

Intermittent claudication is the most characteristic symptom of arteriosclerosis obliterans. In the Framingham study,[3] the clinical manifestations of coronary atherosclerosis were four times more common than intermittent claudication. The incidence of both increased with age, and the onset of symptoms occurred approximately 10 years earlier in men than in women.[3,4]

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TABLE I

Protocol for Exercise Evaluation of Peripheral Arterial Disease

1. Bilateral upper and lower limb blood pressure measurement, Doppler ultrasonic flow, pulse volumes and grading by palpation performed in resting state.
2. Modified lead II of electrocardiogram recorded in resting state.
3. Treadmill testing initiated at 1.7 miles/hour (10 percent grade) and gradually brought up to a speed of 2. 5 miles/hour as tolerated by the patient. A query regarding tolerance offered every 30 seconds. Lead II monitored.
4. Termination of test after appearance of limiting symptoms, abnormal electrocardiographic response or a maximal 5 minutes of exercise.
5. Step 1 repeated immediately after the stress test.
6. Modified lead II of electrocardiogram recorded at 1, 2, 3, 4 and 5 minutes after treadmill exercise.

Coronary artery disease is the leading cause of morbidity and mortality in patients with occlusive peripheral arterial disease. Tomatis et al.[5] demonstrated angiographically significant coronary artery disease in 47 percent of 72 patients with arteriosclerosis obliterans. Lukasik and Liszewska-Pfejfer[6] recently demonstrated with noninvasive techniques an 18.8 percent prevalence rate of peripheral vascular disease in patients with coronary disease. Thirty-four percent of these subjects did not have symptoms compatible with ischemia of the lower limbs.

With the development of refined noninvasive methods for early detection and anatomic characterization of arterial occlusion, treadmill exercise protocols are now routinely utilized in peripheral vascular laboratories. In this study therefore we investigated prospectively the incidence of abnormal electrocardiographic responses in patients undergoing treadmill exercise for the investigation of occlusive peripheral arterial disease.

Methods

Patients: Fifty consecutive patients referred to the peripheral vascular laboratory of this hospital for the evaluation of peripheral arterial disease constituted the study group. There were 30 men and 20 women whose ages ranged from 27 to 88 years (mean 63). They represented the total patient population so investigated from October 1977 to March 1978. All subjects were referred for study because of one of the following complaints: exertional leg cramps or fatigue and paresthesias or pallor of the pedal digits. Eleven of 50 (22 percent) had angiographically documented peripheral vascular disease and a history of prior surgical intervention for this disorder. All patients were questioned regarding clinical symptoms as well as a past or current history of smoking habits, hypertension, diabetes, hyperlipidemia, angina pectoris, myocardial infarction or cerebrovascular disease.

Exercise protocol (Table I): A modified lead II electrocardiogram was recorded before exercise, at the completion of each minute of treadmill testing and every minute from the 1st to the 5th minute after completion of the session. Four patients had abnormal S-T segment changes in the 12 lead electrocardiogram (two with a pattern of complete left bundle branch block and two with a pattern of left ventricular hypertrophy and strain) and were excluded from analysis because of repolarization alterations during exercise.

Pulse volume recordings and systolic segmental arterial pressures were obtained with pneumatic cuffs applied to the lower limbs, which were connected to a pulse volume recorder (Life Sciences, Inc.). A unidirectional Doppler transducer (model 802A, Parks Electronics, Inc.) emitting an ultrasonic frequency of 9.2 megahertz was used to assess the arterial flow dynamic characteristics. All measurements were obtained in the resting state and immediately after the patients exercised on the treadmill.

The end points for testing included symptoms of lower limb disease, the ability to sustain exercise to a limiting grade of 10 percent at 2.5 miles/hour for 5 minutes, and abnormal electrocardiographic changes; the latter included 2 mm of downsloping or horizontal S-T segment depression, salvos of ventricular extrasystoles or a marked increase in the frequency of premature complexes over those in the control tracing.

Results

The prevalence of cardiovascular risk factors and the pertinent associated diseases or symptoms are summarized in Table II for the 50 consecutive patients referred to our laboratory for the evaluation of vascular disease and in Table III for the 32 patients (64 percent) found to have occlusive disease.

Exercise results: Analysis of modified lead II of the electrocardiogram before, during and 1, 2, 3, 4 and 5 minutes after treadmill exercise revealed that the total group of patients had a mean resting heart rate of 78 beats/min and a mean heart rate of 106 beats/min at an average attained speed of 1.9 miles/hour after a mean

TABLE II

Prevalence of Risk Factors and Associated Disease Processes or Symptoms in 50 Patients Referred for Evaluation of Peripheral Arterial Circulation

	Patients	
	no.	%
Cigarette smoking	45	90
Hypertension	14	28
Diabetes mellitus	11	22
Hyperlipidemia	3	6
History of angina pectoris	8	16
Prior myocardial infarction	7	14
Previous cerebrovascular accident	5	10

TABLE III

Prevalence of Risk Factors and Associated Disease Processes or Symptoms in 32 Patients With the Noninvasive Diagnosis of Occlusive Peripheral Arterial Disease

	Patients	
	no.	%
Cigarette smoking	30	93.7
Hypertension	14	43.3
Diabetes mellitus	8	25
Hyperlipidemia	3	9.3
History of angina pectoris	5	15.6
Prior myocardial infarction	5	15.6
Previous cerebrovascular accident	2	6.2

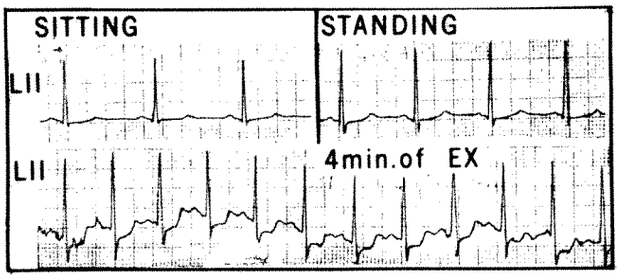


FIGURE 1. Control lead II (LII) electrocardiogram, recorded during sitting and standing, from a 68 year old man with no history of angina pectoris or myocardial infarction. At 4 minutes of treadmill exercise (EX) (2.25 miles/hour, 10 percent grade) there is S-T segment depression suggesting myocardial ischemia.

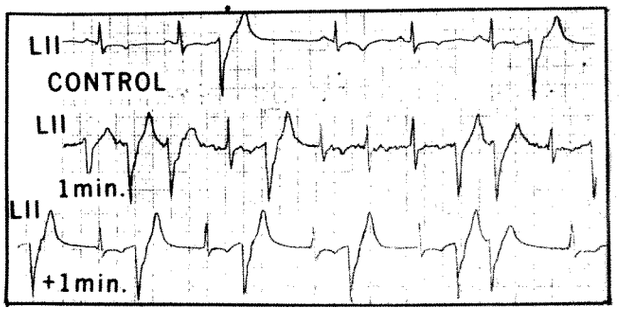


FIGURE 2. Control electrocardiogram (LII) from a 68 year old man with occlusive peripheral arterial disease and no history of angina pectoris or myocardial infarction. The tracing obtained at rest shows S-T segment and T wave abnormalities with occasional premature ventricular complexes. At 1 minute of exercise (1.7 miles/hour, 10 percent grade) salvos of extrasystoles are noted. One minute after termination of the test, ventricular bigeminy and paired premature complexes are recorded. Five minutes after exercise there were only two premature ventricular complexes/min.

exercise duration of 3.8 minutes. At this low work load, corresponding to approximately 63 percent of the predicted maximal heart rate for the mean age of the group, 13 patients (26 percent) had an abnormal electrocardiographic response. Seven patients (five men and two women) (14 percent) manifested S-T segment depression suggestive of myocardial ischemia[7] and six patients (four men and two women) (12 percent) manifested frequent premature ventricular complexes (Fig. 1 and 2). "Frequent" was defined as a rate of occurrence exceeding one premature complex per four sinus complexes.

To ascertain whether peripheral vascular laboratories utilizing treadmill exercise protocols routinely monitor the electrocardiogram during testing, we forwarded a questionnaire to 60 institutions. Of 34 centers responding to the inquiry, only 10 (29 percent) were recording the electrocardiograms of patients being evaluated with exercise testing.

Discussion

The contraindications for submaximal treadmill stress testing in patients with suspected coronary artery disease have been fairly well agreed on, and only some of them can be recognized by means of a resting 12 lead electrocardiogram. Furthermore, in many instances termination of the test is based solely on the electrocardiographic response to exercise.[7] The vast majority of subjects undergoing noninvasive evaluation of peripheral arterial circulation are not stressed to levels that approximate those utilized in submaximal exercise stress tests for assessing myocardial ischemia.

Clinical implications of data: Our data indicate that a substantial number of patients referred to laboratories investigating the peripheral arterial circulation may have abnormal responses to mild degrees of exercise. These findings have both diagnostic and therapeutic implications. Application of continuous electrocardiographic recording during such testing would appear to be useful in identifying a number of patients with concomitant ischemic heart disease. The achievement of an average heart rate of only 106 beats/min suggests that these older patients with suspected or confirmed peripheral arterial disease may have a low ischemic threshold. Alternatively, such a heart rate may connote a fair degree of activity in a study group of patients who, because of their peripheral vascular disease, do not achieve an average exercise range in their daily activities. The S-T segment depression and the development of ventricular ectopy in 26 percent of the study group provide strong evidence that electrocardiographic monitoring should be performed in all subjects referred for exercise evaluation of the peripheral arterial system. Although none of the 50 patients had a cardiac arrest or sustained chest pain as a consequence of exercise, the potential for such events is clear. Patient safety would appear to be a major byproduct of exercise electrocardiographic monitoring in this group.

Clinical application: Less than one third of responding peripheral vascular laboratories indicated that electrocardiographic monitoring was routinely applied in patients referred for the diagnosis of peripheral vascular disease. Universal application of such monitoring would provide a fruitful area for research into the coexistence of ischemic heart disease and occlusive peripheral arterial disease. Additionally, our data imply that resuscitative equipment and staff members well versed in the management of acute cardiac emergencies should be used at such centers. Concomitant electrocardiographic monitoring is used primarily for safety rather than for diagnostic purposes in these patients with suspected peripheral vascular disease.

It should be appreciated by those working in peripheral vascular disease laboratories that associated coronary atherosclerotic heart disease may provide the limiting factor in the exercise testing even though the patients manifest no symptoms of lower limb disease during exercise. Furthermore, the electrocardiographic changes described here are only suggestive rather than specifically diagnostic of myocardial ischemia.

Acknowledgment

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Spectrum of Exercise Thallium-201 Myocardial Perfusion Imaging in Patients With Chest Pain And Normal Coronary Angiograms

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Twenty-seven consecutive patients with chest pain and no significant obstructive coronary lesions on arteriography were studied with thallium-201 myocardial imaging during exercise and at rest. Fifteen of the patients had typical and 12 atypical angina pectoris. All underwent treadmill exercise electrocardiographic testing; the results were abnormal in 10 patients (37 percent), normal in 14 (52 percent) and uninterpretable in 3 (11 percent). The exercise and resting thallium-201 myocardial images were normal in 23 patients (85 percent); the results of exercise testing were normal in 12 of these patients, abnormal in 8 and uninterpretable in 3. Four patients had a perfusion defect on exercise thallium-201 myocardial imaging; the defect filled in by 4 hours in two patients but persisted in the other two. In contrast, when thallium-201 myocardial imaging was performed in 28 consecutive patients with angiographic coronary artery disease, only 5 patients (16 percent) had normal exercise and resting thallium-201 myocardial images. Therefore, thallium-201 myocardial imaging offers a more effective means of identifying patients with chest pain and no obstructive coronary artery disease than the clinical history or the exercise electrocardiographic test, or both. However, 15 percent of these patients will have abnormal exercise thallium-201 myocardial images because of factors that have not yet been identified.

The availability of surgery for patients with coronary artery disease has provoked a marked increase in the use of coronary arteriography to evaluate these patients.[1] It has been suggested that this invasive technique should be performed in every patient with clinical evidence of coronary artery disease.[2] Coronary arteriography is performed in a considerable number of persons with angiographically normal coronary arteries.[3]

To evaluate the noninvasive procedures that might best predict the presence of normal coronary arteries in persons with chest pain, we studied a group of consecutive patients with chest pain and normal coronary arteries. All underwent maximal exercise electrocardiographic testing and myocardial perfusion imaging at rest and on exercise.

Methods

Patients: Twenty-seven patients with chest pain and no obstructive coronary artery disease on coronary angiography were studied. Patients with valvular heart disease or cardiomyopathy were excluded. All patients underwent exercise testing and myocardial imaging with thallium-201 within 72 hours of the time of cardiac catheterization. Echocardiography was also performed in 23 patients. Fourteen patients were men and thirteen women, and their mean age was 49 years (range 30 to 65).

Coronary arteriography: Selective coronary arteriography on 35 mm film in multiple projections, using the Sones or Judkins technique, and left ventric-

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ular angiography were performed in all patients. The results were reported without knowledge of the exercise test, myocardial imaging or echocardiographic findings. Patients with coronary arterial narrowing of 50 percent or greater of the luminal diameter were excluded.

Myocardial perfusion imaging: An intravenous injection of 1.5 mCi of thallium-201 was given at near maximal exercise, 1 to 2 minutes before the exercise was stopped. A total of 500,000 counts images were obtained in the anterior, 30° and 60° left anterior oblique and left lateral projections, using an Ohio Nuclear Series 120 gamma camera with a high sensitivity collimator and set for the 69 to 80 KeV mercury X-ray photonpeak. Images were recorded as Kodak SO-179 transparencies directly from the gamma camera after contrast enhancement from the video display of an Ohio Nuclear Series of 150 Data System. Exercise images were obtained 8 to 12 minutes after exercise in all patients; delayed (rest) images were obtained 4 hours later. Images were interpreted twice by one observer (SJG) without knowledge of the other clinical findings. Regional areas of diminished activity were graded from 1+ to 4+ in contrast to the area of maximal cardiac activity. Regions were classified as anterior, anteroseptal, apical, lateral, inferior and posterior segments. A small band of diminished activity seen in the apical region that was not confirmed in the lateral projection was assumed to be the apical cleft, which has been described as a normal variant.[4]

Exercise test: A Quinton treadmill and Marquette electrocardiograph for recording were used. Twelve lead electrocardiograms were recorded at rest in the supine and standing positions and then after 30 seconds of hyperventilation. A standard Bruce protocol was followed until limiting symptoms or 2 mm S-T segment depression appeared. After the injection of thallium-201 at peak exercise, exercise was continued for 1 to 2 minutes. The 12 lead electrocardiogram and indirect brachial arterial blood pressure were recorded every minute during and after exercise until the symptoms or electrocardiographic ischemic changes resolved. At this point the imaging was started.

The criteria to interpret a test as abnormal were: the development of at least 1 mm of horizontal or downsloping S-T segment depression or at least 2 mm of upsloping S-T depression at 0.08 second after the J point of the QRS in at least three consecutive complexes. The tests were interpreted without knowledge of the patient's coronary arteriographic or thallium-201 imaging results.

The echocardiograms were performed in 23 patients using commercially available equipment and standard techniques.

Results

Clinical features of patients: Fifteen patients (6 men and 9 women) had a history of angina pectoris, that is, chest pain provoked by exercise and relieved by rest or nitroglycerin. The other 12 patients (8 men and 4 women) had episodes of chest pain considered atypical of angina pectoris, that is, pain unrelated to exertion or emotions and not relieved by nitroglycerin or lasting longer than 30 minutes, or both. Seventeen patients were treated for chest pain; nitroglycerin was administered in 4 patients, propranolol in 7 and both in 6. One patient received digitalis for dyspnea.

The resting electrocardiogram was normal in 18 patients. Seven patients had nonspecific S-T segment and T wave abnormalities, one had left bundle branch block and one left anterior hemiblock. No patient had a myocardial infarction pattern.

In the exercise test, 14 of the 27 patients achieved the maximal heart rate predicted for their age and sex; 9 patients achieved a heart rate greater than 85 percent of the maximal predicted rate and 4 achieved a rate of 70 to 85 percent of the maximal predicted rate (3 of these were receiving propranolol). The results of the exercise test were normal in 14 patients, abnormal in 10 and uninterpretable in 3 (1 patient with left bundle branch block, 1 with marked S-T changes on hyperventilation and 1 patient who was receiving digitalis). The results of the exercise test were abnormal in 10 patients; 6 of these patients had a history of angina pectoris, but only 1 had chest pain during the test (Fig. 1).

Echocardiography was performed in 23 patients, with normal results in 17. Five patients had mild left ventricular hypertrophy (posterior wall or septal thickness or both, of 12 to 13 mm), and one had mitral valve prolapse (late systolic hammocking). None of the six patients with an abnormal echocardiogram had an abnormal thallium-201 image. The results of the exercise test were abnormal in one of the 5 patients with mild left ventricular hypertrophy and in the patient with mitral valve prolapse.

Angiographic findings: Twenty-six patients had a normal left ventriculogram and 1 (the patient with left bundle branch block) had anterior wall asynchrony. No patient had angiographic evidence of mitral valve prolapse. Twenty-three patients had normal and smooth coronary arteries, and 2 had minimal irregularities of the right coronary artery. Two patients had 10 to 30 percent obstructive lesions of the proximal left anterior descending coronary artery, and both had normal myocardial perfusion images.

Thallium-201 imaging: When the intraobserver interpretations of each patient's myocardial images were compared, no significant differences were found.

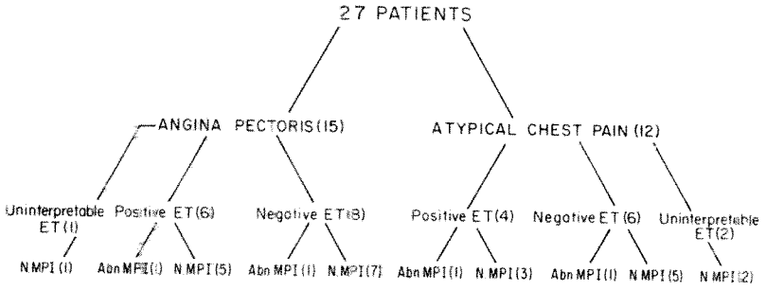


FIGURE 1. Distribution of the exercise test (ET) and myocardial perfusion imaging (MPI) findings among the 15 patients with angina pectoris and the 12 patients with atypical chest pain. Abn = abnormal; N = normal.

TABLE I

Abnormal Myocardial Perfusion Imaging in Four Patients With Normal Coronary Arteries*

Case no.	Age (yr) & Sex	Pain	ECG	ET	R-TI	Ex-TI
1	43M	Atypical	N	Abn	N	Abn
2	47F	Angina	S-T & T	N	N	Abn
3	58F	Angina	N	Abn	Abn	Abn†
4	46M	Atypical	N	N	Abn	Abn†

* Echocardiographic and left ventriculographic results were normal in all four patients.
† Rest and exercise myocardial perfusion imaging was repeated 6 months later with similar findings.
Abn = abnormal; ECG = electrocardiogram; ET = exercise test; Ex-TI = exercise thallium-201 myocardial perfusion image; N = normal; R-TI = resting thallium-201 myocardial perfusion image; S-T & T = S-T segment and T wave abnormality.

Twenty-three patients had normal resting and exercise thallium-201 perfusion images (Fig. 1). Two patients had a defect at rest that increased with exercise; in both patients a repeat exercise and resting thallium-201 myocardial perfusion test was performed 6 months after the first test, with the same findings. In two patients, the resting thallium-201 image was normal, but during exercise, a defect was evident in the anteroseptal areas in both patients and also in the lateral wall in one patient. No pattern was observed among the patients with an abnormal thallium-201 image; one patient had angina pectoris and abnormal exercise test results, one patient had angina and normal exercise test results, and two patients had atypical chest pain (Table I). The echocardiogram and left ventriculogram were normal in these four patients. Representative resting and exercise electrocardiograms and thallium-201 myocardial image tests are shown in Figures 2, 3 and 4.

The combination of a normal electrocardiographic exercise test and normal resting and exercise thallium-201 myocardial perfusion images was found in only 12 of our patients (44 percent). This combination was not a better predictor of the absence of obstructive coronary artery disease in our patients than the isolated use of myocardial perfusion imaging (Fig. 5 and 6).

Discussion

Myocardial perfusion imaging with thallium-201 provides a useful noninvasive method for detecting the distribution of myocardial blood flow.[5–7] Normal left

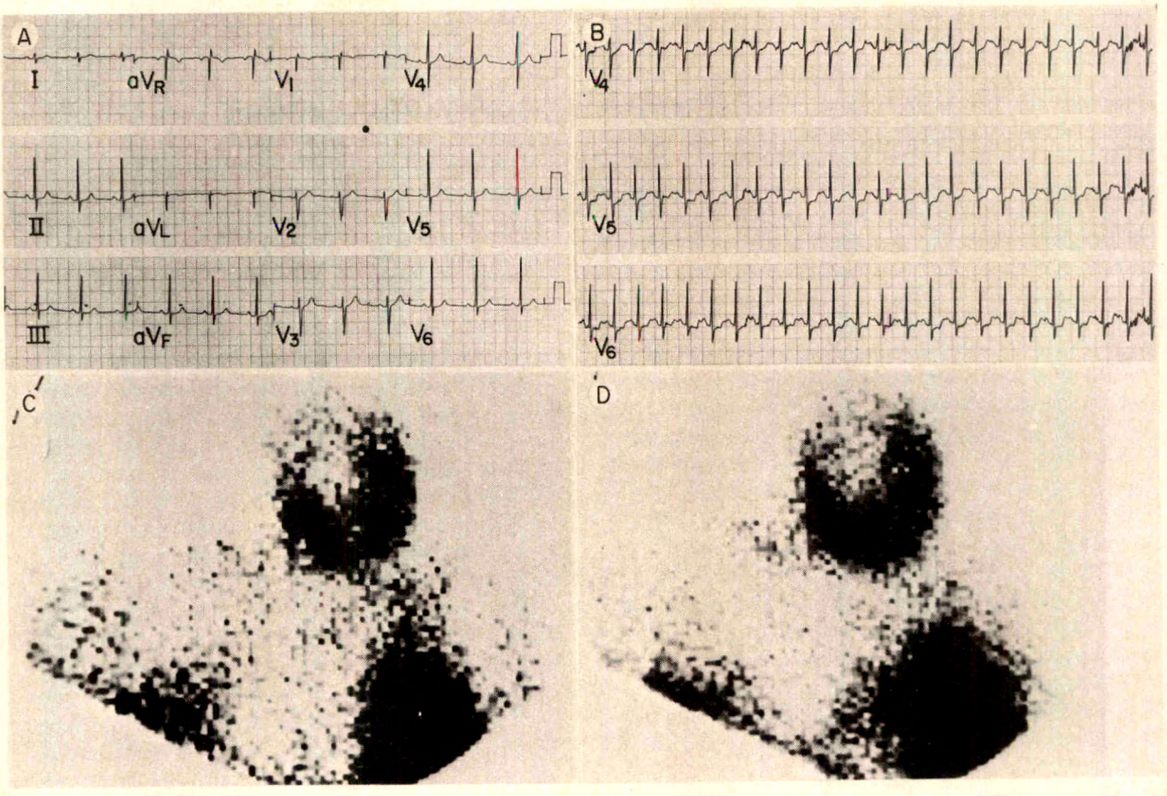


FIGURE 2. Representative findings at rest and during exercise in a patient with normal coronary arteries and a normal electrocardiogram at rest (**A**), an abnormal exercise test (**B**) and normal perfusion images at rest (**C**) and during exercise (**D**).

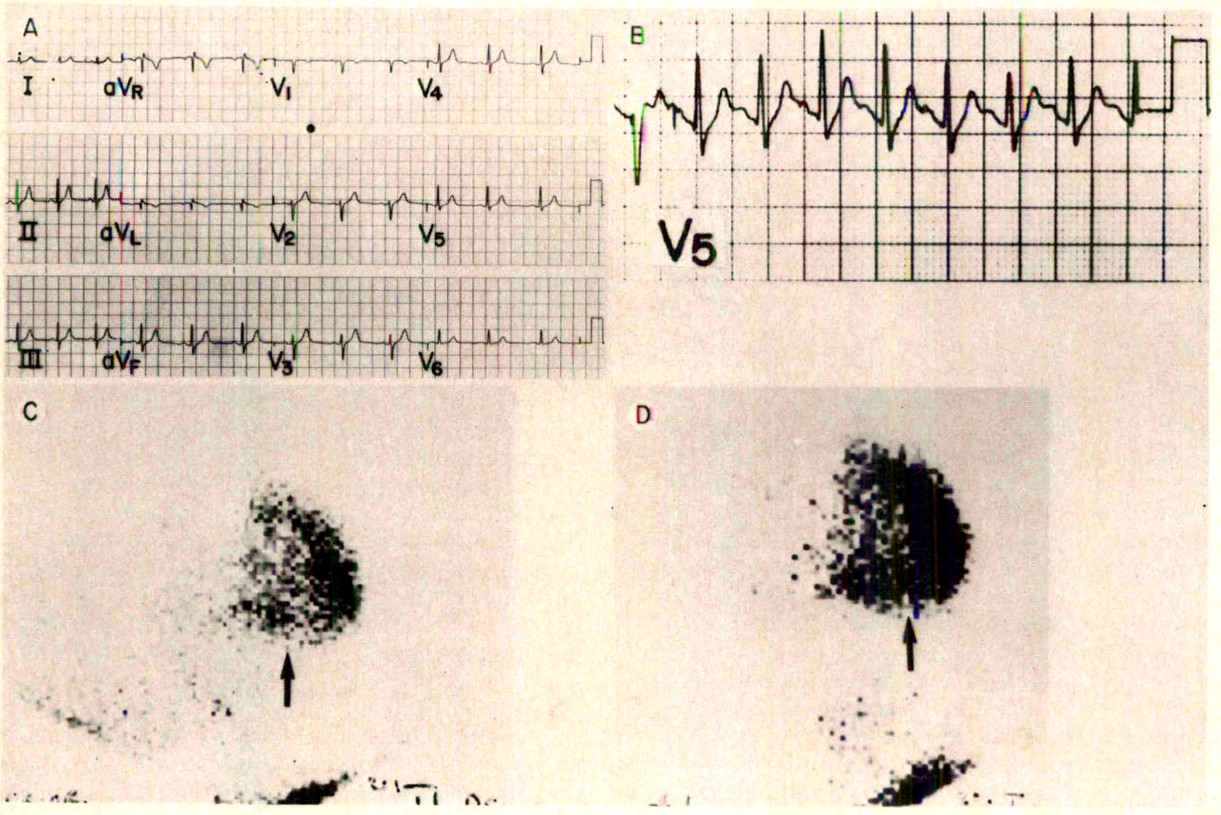


FIGURE 3. Representative findings at rest and during exercise in a patient with normal coronary arteries and a normal electrocardiogram at rest (**A**), a normal exercise test (**B**) and inferior wall perfusion on imaging (**arrows**) that is borderline abnormal at rest (**C**) (decreased perfusion compared with other walls) and definitely abnormal during exercise (**D**).

ventricular perfusion at rest has been found to be a good predictor of normally functioning myocardium, irrespective of the presence and degree of coronary artery disease.[8] Decreased segmental concentration of thallium-201 compared with normally perfused areas during exercise suggests transient myocardial ischemia if no perfusion defect is found at rest.[9,10] Myocardial infarction or infiltration is suggested if the defect present on exercise is persistent at rest.[5,8,9,11]

Several studies found a good correlation between resting and exercise myocardial perfusion imaging with thallium-201 and the ventriculographic and coronary arteriographic data in patients with coronary disease.[6,8,12,13] The normal subjects in these studies had normal rest and exercise myocardial perfusion images.[6] The nine patients with exertional chest pain, an abnormal exercise treadmill test and normal coronary arteries on arteriography reported on by Raphael et al.[14] also had normal thallium-201 myocardial perfusion images. In patients with mitral valve prolapse and normal coronary angiograms, the results of rest and exercise scintigraphy are controversial. Although Massie et al.[15] and Gaffney et al.[16] reported normal stress thallium-201 or rubidium-81 perfusion images in 19 and 11 patients, respectively, with mitral valve prolapse, Staniloff et al.[17] found that 11 of their 20 patients with this diagnosis had abnormal thallium-201 tests. Only one of our patients had mitral valve prolapse, and he had a normal perfusion image.

Normal thallium-201 imaging as a predictor of absence of obstructive coronary artery disease: Our study demonstrates that no combination of the noninvasive tests used was more accurate in predicting the absence of obstructive coronary artery disease in patients with chest pain than myocardial perfusion imaging alone at rest or during exercise, or both (Fig. 5 and 6). A high incidence rate of false-positive diagnoses occurred with the use of clinical history of angina pectoris (55 percent) and exercise treadmill tests (37 percent). The electrocardiogram was normal in 66 percent of these patients; however, it is well known that a normal electrocardiogram correlates well with a normal left ventriculogram but poorly with the absence of coronary artery disease.[18] If myocardial infarction has occurred, the echocardiogram may be abnormal,[19] but if left ventricular function is preserved a normal echocardiogram would be expected irrespective of the state of the coronary arteries.

Exercise myocardial perfusion imaging with thallium-201 disclosed no evidence of abnormal myocardial blood flow distribution in 23 of the 27 patients (85 percent) with chest pain and normal coronary arteries. The cause of abnormal myocardial perfusion imaging in the other four patients is unclear. No evidence of left

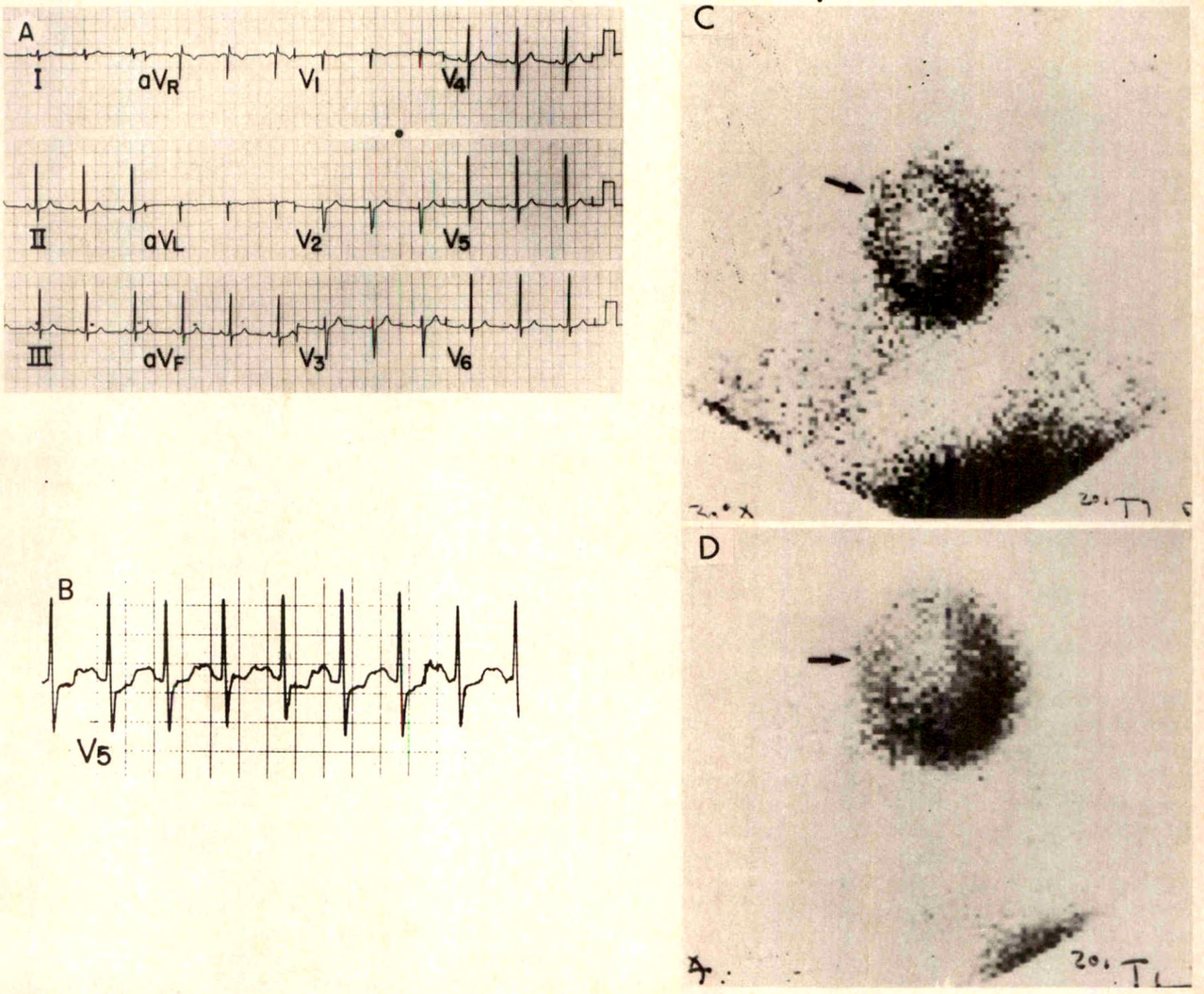


FIGURE 4. Representative findings at rest and during exercise in a patient with normal coronary arteries and a normal electrocardiogram at rest (**A**), an abnormal exercise test (**B**) and anteroseptal wall perfusion on imaging (**arrows**) that is borderline abnormal at rest (**C**) (decreased perfusion compared with other walls) and definitely abnormal during exercise (**D**).

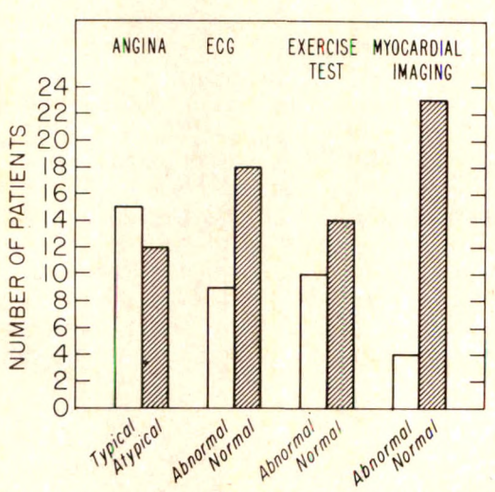


FIGURE 5. Summary of chest pain history and results of the noninvasive tests performed in the 27 patients with normal coronary arteries. ECG = electrocardiogram.

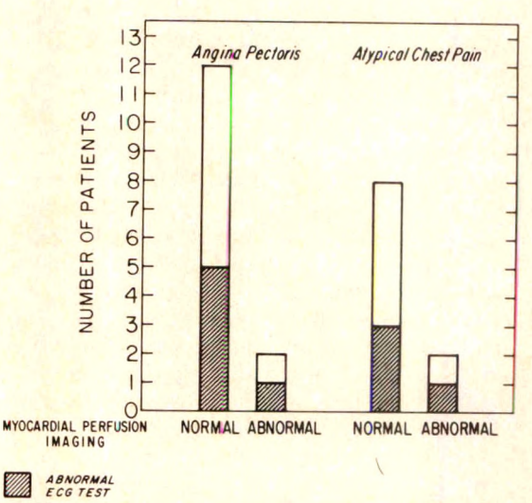


FIGURE 6. Combination of myocardial perfusion imaging and electrocardiographic (ECG) exercise test in 27 patients with chest pain and normal coronary arteries.

ventricular hypertrophy or mitral valve prolapse was found on echocardiography, and only two patients had an abnormal exercise electrocardiographic test. Although small inhomogeneities of thallium-201 uptake have frequently been found in normal persons,[6] most investigators have not found myocardial perfusion images that are clearly abnormal in similar patients.[6,14,20] McLaughlin et al.[12] noted one instance of a perfusion defect in an inferior segment supplied by a normal right coronary artery; however, that patient had significant obstruction of the left circumflex artery, and overlap of perfusion territory could have been present. Okada et al.[21] reported that, among 11 patients with no coronary artery disease, 1 patient had a positive and 2 had equivocal thallium-201 studies.

None of our patients had an apical perfusion defect. In scintigrams of dog hearts, the apex frequently appears thinner than the rest of the myocardium, probably because of the configuration of the ventricular muscle in the area rather than because of decreased myocardial perfusion.[20,22] In humans, an apical cleft is considered a normal finding.

Significance of an abnormal perfusion image: The abnormal myocardial perfusion image may be a false finding caused by a limitation of the technique, such as field nonuniformity or variations of the normal pattern with no uniform perfusion in nonischemic segments.[20] We evaluate a uniform radioactive source daily, and thus field nonuniformity is unlikely.

The abnormal myocardial perfusion image may also be a true finding of a perfusion deficit during exercise that does not depend on fixed coronary arterial obstruction, such as inadequate segmental supply of blood, segmental myocardial hypertrophy or coronary arterial spasm. The abnormal image may also be a true finding indicating a misinterpretation of the coronary angiograms. Our four patients with abnormal myocardial perfusion images had completely normal and smooth coronary arteries, and no vessels appeared to be missing or completely obstructed. Because two of these patients had a repeat rest and exercise myocardial perfusion imaging test with the same abnormal segmental findings as in the first test, it appears unlikely that these patients had coronary arterial spasm. Because Korhola et al.[23] found regional perfusion abnormalities on xenon-133 scintigraphy in 10 of 20 patients with angina, a positive exercise test and normal coronary arteries, the patients might have had truly compromised flow rather than a metabolic disorder. Future studies combining thallium-201 and xenon-133 imaging might further characterize these patients and differentiate varying abnormalities in pathways of isotope uptake.

Significance of a normal perfusion image: A normal exercise myocardial perfusion image does not automatically predict the absence of coronary artery disease. Sixteen percent of our patients with coronary disease[8] had normal thallium scans, whereas Bailey et al.[6] found that 25 percent of their patients with coronary artery disease had normal resting and exercise myocardial perfusion imaging. More accurate myocardial imaging can be obtained with intracoronary labelled macroaggregated albumin than with thallium-201.[24] It has been demonstrated that the sensitivity of the myocardial perfusion imaging test to coronary artery disease is directly related to the number of coronary vessels obstructed[6] and that the test is least sensitive to significant obstructive disease of the left circumflex coronary artery.[12] In some patients with coronary artery disease, ischemia may develop with exercise in one region and cause symptoms before ischemia occurs in a second region supplied by another obstructed coronary artery.[25] If the exercise is submaximal, some perfusion defects may be missed[12]; if the perfusion deficit is less than 45 percent of the increased perfusion of normal myocardium[20] or if the defect is small, the scan may appear normal. A uniform reduction of tracer uptake with severe proximal triple vessel disease could also explain the lack of transient segmental perfusion defects in some patients.[26]

Clinical implications: It has been suggested that myocardial perfusion imaging is crucial in predicting the presence of coronary artery disease in asymptomatic individuals with ischemic S-T segment depression on exercise[27] or, in general, in aiding the differentiation of false-positive and false-negative exercise tests.[28,29] Our findings indicate that the exercise thallium-201 myocardial perfusion imaging test is a good noninvasive detector of normal coronary arteries in patients with chest pain. However, in testing for the presence of coronary atherosclerosis, 15 percent of the results are false-positive. The perfusion deficits found may reveal forms of ischemic heart disease other than atherosclerotic disease. This decreased specificity may be a limiting factor in evaluating a patient for coronary atherosclerosis, but if such abnormal scans can be correlated with other evidence of myocardial ischemia such as regional left ventricular dysfunction, the test will have added significance in the evaluation of patients with chest pain and proved normal coronary angiograms.

Addendum

Since submission of this paper, a multicenter study with myocardial imaging with thallium-201 in 190 patients with angina pectoris was published in this Journal (Ritchie JL, Zaret BL, Strauss HW, Pitt B, Berman DS, Schelbert HR, Ashburn WL, Berger HJ, Hamilton GW: Myocardial imaging with thallium-201: a multicenter study in patients with angina pectoris or acute myocardial infarction. Am J Cardiol 42:345–350, 1978). Of the 42 patients with no or insignificant coronary artery disease, 3 were thought to have definite false positive studies.

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Reproducibility of Exercise-Induced Ventricular Arrhythmia After Myocardial Infarction

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To evaluate the reproducibility of exercise-induced ventricular arrhythmia, 155 men with a mean age of 53 ± 8 years underwent serial exercise testing 3 to 52 weeks after myocardial infarction. The reproducibility of categorical test responses, that is, the presence or absence of ventricular arrhythmia, was evaluated with the kappa coefficient, which considers negative as well as positive test responses and expresses reproducibility above the chance level. Reproducibility was highest at an intertest interval of 1 to 5 days and was not enhanced by further categorizing premature ventricular complexes as simple or complex based on their frequency or configuration. Continuous response measures such as frequency of premature ventricular complexes yielded higher reproducibility than categorical responses. Continuous response measures appear preferable to categorical responses for evaluating the clinical significance and response to antiarrhythmic therapy of ventricular arrhythmias.

Exercise testing is often used diagnostically to elicit premature ventricular complexes and to evaluate their clinical significance, including their response to various forms of treatment.[1–24] Recent studies[1,11–14,21] indicated that individual patients may exhibit marked spontaneous variability in exercise-induced ventricular arrhythmias. Although some of the factors responsible for this variability are due to differences in patient selection, other factors are inherent in the test method and can be modified to yield optimal reproducibility.

The purpose of this study is twofold: (1) to evaluate the reproducibility of exercise-induced ventricular arrhythmias using uniform, standardized methods to elicit premature ventricular complexes; and (2) to compare the effects of various methods used to express the reproducibility of exercise-induced ventricular arrhythmia.

Methods

Patients: One hundred and fifty-five men less than 70 years of age hospitalized at the Stanford Medical Center for treatment of acute myocardial infarction were selected for this study. Myocardial infarction was documented by a history of prolonged chest pain consistent with infarction, the appearance of new Q waves or evolutionary ST-T changes and characteristic elevation of cardiac enzymes. Patients with one or more of the following characteristics 3 weeks after hospital admission were not included: (1) rest angina or unstable angina, (2) clinical congestive heart failure or the presence of a ventricular diastolic gallop, and (3) associated medical conditions such as significant valvular heart disease, hypertension greater than 180/100 mm Hg, or limiting pulmonary disease or musculoskeletal abnormalities.

The mean age of the population was 53 ± 8 years. The infarction was inferior transmural in 62 percent of the patients, anterior transmural in 29 percent and nontransmural in 9 percent. The peak creatine kinase elevation was 872 ± 692 IU/liter and the peak serum glutamic oxaloacetic transaminase elevation 111 ± 82 IU/liter. Within the first 5 days of hospitalization, 28 percent of the patients

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had ventricular tachycardia or ventricular fibrillation, and 5 percent had radiographic evidence of heart failure. Eight percent of the patients had a history of previous myocardial infarction. Twenty-five percent received antiarrhythmic medication at some time during the study: propranolol (25 patients), quinidine (9 patients) or procainamide (4 patients), or a combination of at least two of these (9 patients). All medications were withheld for 16 to 24 hours before testing. Patients did not undergo formal exercise training during this study.

Exercise testing protocol: Patients underwent serial treadmill exercise testing at 3, 5, 7, 9 and 11 weeks and 6 and 12 months after myocardial infarction. Forty patients underwent two treadmill tests within 1 week at 3 and 11 weeks after myocardial infarction. Before testing, patients were interviewed and examined by a physician, and informed consent was obtained. A physician or a specially trained nurse conducted the test. Exercise was performed on a motor-driven treadmill, using a combination of protocols described by Naughton et al.[25] (Table I). Tests were performed at least 2 hours after eating or smoking. Exercise began at a workload equivalent to three multiples of resting energy expenditure (METs).

The work load was increased every 3 minutes until any of the following end points appeared: (1) limiting symptoms of chest pain, dyspnea, fatigue, leg cramps or dizziness; (2) hypotension, that is, a decrease in systolic blood pressure of 10 mm Hg or more from the peak value attained earlier during exercise; and (3) ventricular tachycardia, that is, three or more consecutive premature ventricular complexes. Neither the attainment of an age-predicted maximal heart rate nor the magnitude of ischemic S-T segment depression alone was used as an end point for the test. Twelve lead electrocardiograms were recorded at rest, at the end of each 3 minute stage of exercise and at 1, 3, 5, 7 and 10 minutes of recovery. In addition, leads V_4 to V_6 were continuously displayed on a three channel oscilloscopic monitor and recorded on magnetic tape for 3 minutes before exercise and during the entire period of exercise and recovery. At the same time, a trained technician recorded, minute by minute, the premature ventricular complexes observed on the oscilloscope. Patients were considered to have ischemia when 1 mm or more of S-T segment depression was induced by exercise. Ventricular ectopy was considered absent when no premature ventricular complexes occurred during exercise or the 10 minute recovery period. Ventricular ectopy was further classified as simple or complex, using various definitions based on the frequency and configuration of premature ventricular complexes.

TABLE I

Treadmill Protocol

Speed (miles/hr)	Grade (%)	METs
2	0	2
2	3.5	3
2	7.0	4
2	10.5	5
2	14.0	6
2	17.5	7
3	12.5	8
3	15.0	9
3	17.5	10
3	20.0	11
3	22.5	12

METs = estimated multiples of resting energy expenditure.

Statistical analysis: *The reproducibility of categorical test responses,* either two category (absence versus presence) or three category (absence versus simple versus complex ventricular ectopy), was measured with the kappa coefficient. This is a quantitative measure of the reproducibility of categorical responses above the chance level.[26–28] The kappa coefficient varies from 0.0 (no reproducibility above the chance level) to 1.0 (perfect reproducibility).[26]

The utility of the kappa coefficient as a measure of test-retest reproducibility was previously demonstrated.[27,28] We used the McNemar test[29] to evaluate the change in the prevalence of premature ventricular complexes from test to test. The calculation of various measures used to evaluate the reproducibility of two category (absence versus presence) and three category (absence versus simple versus complex) responses is shown in the Appendix.

Correlation coefficients were used to evaluate the reproducibility of continuous test responses such as peak frequency and heart rate at the onset of premature ventricular complexes. Tests at 11 weeks and 6 months were used for such evaluations. The peak frequency of premature ventricular complexes, that is, their maximal number per minute, correlated well with the total number of premature ventricular complexes during the tests: In 25 randomly selected patients the correlation coefficient between peak frequency and total number of premature ventricular complexes was 0.46 ($P < 0.05$). Heart rate at the onset of premature ventricular complexes was expressed as a percent of the age-predicted maximal value.[30] When premature ventricular complexes were present at rest, the resting heart rate was used for this determination. When premature ventricular complexes were absent at rest, the heart rate at the onset of ventricular ectopy during exercise was used. When premature ventricular complexes were absent during all three periods of the test or appeared only during recovery, the maximal heart rate during exercise was used.

TABLE II

Prevalence of Exercise-Induced Premature Ventricular Complexes Versus Intertest Interval

Intertest Interval	Sample Size (no.)	Prevalence T_1	Prevalence T_2	Prevalence Change, McNemar Test
1–5 days				
Week 3*	37	0.32	0.43	0.90 (NS)
Week 11*	30	0.43	0.50	0.17 (NS)
2 weeks				
Weeks 3–5*	22	0.27	0.50	1.78 (NS)
Weeks 5–7*	20	0.45	0.55	0.50 (NS)
Weeks 7–9*	23	0.61	0.70	0.17 (NS)
Weeks 9–11*	34	0.62	0.70	0.57 (NS)
4 weeks				
Weeks 7–11*	104	0.55	0.54	0.00 (NS)
8 weeks				
Weeks 3–11*	124	0.33	0.54	14.20 ($P < 0.01$)
3 months				
Months 3–6*	135	0.52	0.52	0.00 (NS)
Months 6–9*	71	0.52	0.59	0.64 (NS)
Months 9–12*	59	0.58	0.55	0.05 (NS)
6 months				
Months 3–9*	106	0.49	0.50	0.00 (NS)

* Time after myocardial infarction.
NS = probability (P) not significant; T1 = Test 1; T2 = Test 2.

TABLE III

Reproducibility of Exercise-Induced Ventricular Arrhythmia

Intertest Interval	Sample Size (no.)	Two Category Response: Percent Reproducibility Absent PVC	Two Category Response: Percent Reproducibility Present PVC	Two Category Response: Kappa Coefficient	Three Category Response: Percent Reproducibility Absent PVC	Three Category Response: Percent Reproducibility Simple PVC	Three Category Response: Percent Reproducibility Complex PVC	Three Category Response: Kappa Coefficient
1–5 days								
Week 3*	37	72	75	0.44†	72	63	75	0.44†
Week 11*	30	76	85	0.57†	76	43	83	0.51†
2 weeks								
Weeks 3–5*	22	56	67	0.18 (NS)	56	0	100	0.26 (NS)
Weeks 5–7*	20	82	100	0.80†	82	0	57	0.43†
Weeks 7–9*	23	56	86	0.43†	56	13	83	0.23 (NS)
Weeks 9–11*	34	62	90	0.54†	62	40	50	0.30‡
4 weeks								
Weeks 7–11*	104	66	70	0.36†	66	37	60	0.33†
8 weeks								
Weeks 3–11*	124	58	78	0.31†	58	58	50	0.28†
3 months								
Months 3–6*	135	68	68	0.37†	68	48	48	0.34†
Months 6–9*	71	56	68	0.24†	56	43	56	0.26†
Months 9–12*	59	64	65	0.32†	64	44	86	0.41†
6 months								
Months 3–9*	106	69	69	0.38†	69	46	54	0.35†

* Time after myocardial infarction.
† P (probability) <0.01.
‡ $P<0.05$.
NS = probability not significant; PVC = premature ventricular complexes.

Results

Prevalence of exercise-induced ventricular arrhythmia: The mean prevalence rate of exercise-induced ventricular arrhythmia in our study patients was 52 percent. Table II lists the prevalence of exercise-induced ventricular arrhythmia at various intertest intervals. Except for the 3 to 11 week test pairs, the prevalence of premature ventricular complexes did not change significantly in the 1 year after infarction. Three to 5 weeks after infarction, the prevalence rate of premature ventricular complexes nearly doubled and might have produced a significant McNemar test if the sample

TABLE IV

Reproducibility of Exercise-Induced Ventricular Arrhythmias Using Various Definitions for Simple and Complex Premature Ventricular Complexes (PVC)

Definition	Sample Size (no.)	Percent Reproducibility Absent PVC	Percent Reproducibility Simple PVC	Percent Reproducibility Complex PVC	Kappa Coefficient
Simple, ≤3 PVC/min; complex, >3 PVC/min	135	68	47	52	0.33*
Simple, ≤4 PVC/min; complex, >4 PVC/min	135	68	50	47	0.33*
Simple, ≤5 PVC/min; complex, >5 PVC/min	135	68	54	45	0.34*
Simple, ≤3 PVC/min; complex, >3 PVC/min or presence of bigeminy, couplets or VT	135	68	48	48	0.34*
Simple, any no. of isolated PVC; complex, >3/min and presence of bigeminy, couplets or VT	135	68	56	44	0.34*
Simple, any no. of isolated PVC; complex, bigeminy or couplets or VT	135	68	59	43	0.36*

* $P<0.01$.
VT = ventricular tachycardia.

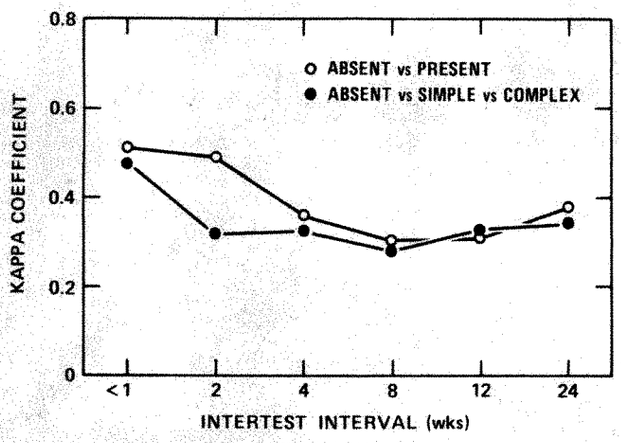


FIGURE 1. Reproducibility (kappa coefficient) of two category (absence versus presence) and three category (absence versus simple versus complex) responses as a function of the intertest interval. wks = weeks.

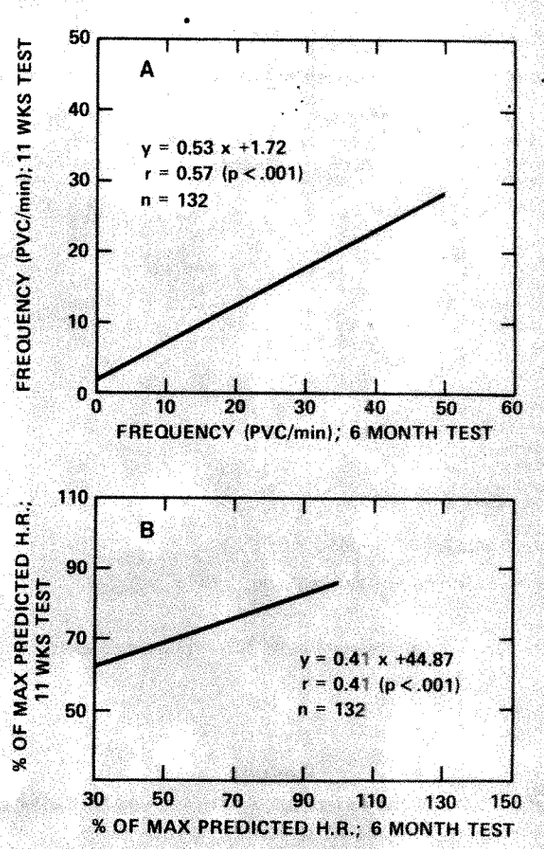


FIGURE 2. Reproducibility of continuous test responses. **A**, correlation coefficients for peak frequency of premature ventricular complexes (PVC) (maximal number of PVC/min) for 11 week and 6 month tests. **B**, correlation coefficient for heart rate at onset of premature ventricular complexes expressed as a percent of the age-predicted maximal heart rate (H.R.) for 11 week and 6 month tests. p = probability; WKS = weeks.

size had been larger. This change in prevalence may reflect the inability of patients to achieve a sufficiently high heart rate at 3 weeks to disclose premature ventricular complexes that are evident on later testing. The mean maximal heart rate achieved 3 weeks after infarction was 112 ± 11 beats/min (mean ± standard deviation) compared with 123 ± 18 beats/min at 5 weeks (P <0.05) and 145 ± 20 beats/min at 11 weeks (P <0.05 versus the value at 5 weeks). No significant changes in maximal heart rate were noted for other intertest intervals.

The reproducibility of categorical test responses: Table III shows the reproducibility of exercise-induced premature ventricular complexes characterized as two or as three category responses. Only the 3 to 5 week test pair failed to demonstrate a significant kappa coefficient of reproducibility, reflecting in part the previously noted change in the prevalence of premature ventricular complexes. When exercise-induced ventricular arrhythmia was further classified as simple or complex, reproducibility was generally not enhanced. For example, when ventricular arrhythmia was defined as complex based on a frequency rate of 4 premature ventricular complexes/min or on the presence of bigeminy, couplets or ventricular tachycardia, the kappa coefficient was generally less than that computed for two category responses at the same intertest interval (Table III). Similarly, reproducibility was not enhanced when data were reanalyzed using various definitions of complex ventricular arrhythmias (Table IV). Multifocal configuration was not used as a criterion for complex arrhythmia because of the difficulty of detecting it at the relatively high heart rates noted with exercise testing. However, it is likely that most tests with multifocal premature ventricular complexes demonstrated other features of complex arrhythmias.[1,31]

Figure 1 illustrates the effects of the intertest interval on reproducibility. Reproducibility was highest at an interval of 1 to 5 days and gradually decreased at longer intertest intervals. Two category responses demonstrated a slight advantage over three category responses, especially at shorter intertest intervals.

Reproducibility of continuous test responses (Fig. 2): The peak frequency of premature ventricular complexes at 11 weeks and at 6 months correlated significantly (r = 0.57, P <0.001). Moreover, within the group of patients with premature ventricular complexes, the average peak frequency per minute did not change significantly within this interval: 7 ± 9 (mean ± standard deviation) versus 5 ± 9 premature ventricular complexes/min at 11 weeks and 6 months, respectively. The correlation coefficient for the heart rate at the onset of ventricular ectopy at 11 weeks and at 6 months was 0.41 (P <0.001). Similarly, the average percentage of age-predicted heart rate at the onset of ventricular ectopy did not change significantly 11 weeks to 6 months after infarction: 116 ± 26 beats/min (mean ± standard deviation) versus 119 ± 25 beats/min.

Discussion

Exercise testing has long been used to disclose ventricular ectopy.[1-24] An apparent deficiency of this method for diagnosing ventricular ectopy is its poor reproducibility, as reported by several authors.[1,12-14,24] These reports appear to present an unduly pessimistic view of the ability of exercise testing to disclose ventricular ectopy. The standardization of exercise test methods, the measurement of ventricular ectopy at optimal intertest intervals and the use of optimal methods for expressing reproducibility probably enhance the value of exercise testing in the clinical evaluation of ventricular ectopy.

Our study group consisted of men free of clinically significant ventricular dysfunction who underwent symptom-limited testing performed at uniform intervals after myocardial infarction. Under these standardized circumstances, the kappa coefficient for exercise-induced ventricular arrhythmia averaged 0.3 to 0.5, depending on the intertest interval. This degree of reproducibility is significantly greater than the chance level and is therefore clinically useful. Koran[28] evaluated the reproducibility of many of the commonly used clinical and laboratory methods and found that the kappa coefficient ranged from 0.3 to 0.6.

Factors influencing reproducibility of exercise-induced ventricular arrhythmias: Tests were conducted at various intervals to assess the effect of the intertest interval on the reproducibility of premature ventricular complexes. A higher reproducibility of exercise-induced ventricular arrhythmia was found when treadmill tests were performed at relatively short intervals, that is, within 2 weeks for two category responses (absence versus presence) and within 1 week for three category responses (absence versus simple versus complex). These intervals are likely to be encountered in the evaluation of antiarrhythmic drug therapy and therefore appear more clinically relevant than the longer intervals of 5 and 2.9 years studied by Blackburn et al.[20] and Faris et al.,[12] respectively, or the very short intervals of 45 minutes studied by Sheps et al.[14]

The reproducibility of exercise-induced ventricular arrhythmia in our patients, expressed as the kappa coefficient, was not enhanced by further classifying ventricular arrhythmia as simple or complex using various definitions for each. These results differ from those of Jelinek and Lown,[1] who reported that the reproducibility of complex ventricular arrhythmias, that is, ventricular tachycardia and couplets, was higher (50 percent) than that of all premature ventricular complexes (30 percent). Similarly, DeBacker et al.[13] found the reproducibility of frequent premature ventricular complexes (greater than 7/min) higher (92 percent) than that of all premature ventricular complexes (82 percent) or couplets (35 percent) or ventricular tachycardia (17 percent). These discrepancies largely reflect differences in patient selection and in the method of expressing reproducibility. Jelinek and Lown and DeBacker et al. considered only patients with a positive first test, whereas half of our patients had a negative first test. Moreover, these authors evaluated only unidirectional changes (from positive to negative), whereas we considered bidirectional changes (from positive to negative *and* from negative to positive).

Use of the kappa coefficient permits evaluation of the *entire* population. Whereas most interest in reproducibility has focused on patients with a positive first test, it is often clinically important to be sure that the absence of ventricular ectopy is also reproducible. Moreover, the kappa coefficient expresses changes in relation to the changes expected by chance alone. A further advantage of the kappa coefficient is that it expresses reproducibility as a single number from 0 to 1 and is less cumbersome than other clinically available methods for expressing reproducibility. Therefore the kappa coefficient appears more clinically useful than other previously reported methods for expressing the reproducibility of categorical test responses.

The reproducibility of continuous responses, that is, the frequency of premature ventricular complexes and heart rate at the onset of ventricular ectopy, was significant despite the relatively long intertest interval of 3 months. Shorter intertest intervals might yield even higher reproducibility. DeBacker et al.[13] noted a high correlation coefficient ($r = 0.80$) between the frequency of premature ventricular complexes in two tests 2 weeks apart. Sheps et al.[14] also reported a high correlation coefficient ($r = 0.98$) between the frequency of premature ventricular complexes in two consecutive tests 45 minutes apart. If, after test conditions are optimized, the reproducibility of ventricular arrhythmias in a given population is still not satisfactory, the use of a larger sample size or the pooling of multiple test results will enhance the clinical reliability of exercise-induced premature ventricular complexes.[32,33]

Clinical implications: (1) The reproducibility of categorical responses is best estimated by the kappa coefficient, which considers bidirectional variations in test results and expresses reproducibility above the chance level. The highest reproducibility is achieved at relatively short intertest intervals, a factor that should be considered in evaluating antiarrhythmic therapy. (2) The further classification of categorical test responses into simple and complex categories based on the frequency of premature ventricular complexes or morphology does not appear to enhance reproducibility. (3) For the same intertest interval, continuous response measures such as the frequency of premature ventricular complexes or heart rate at the onset of ventricular ectopy appear more reproducible than categorical responses. This suggests that continuous measures may be more sensitive than categorical ones and may therefore be a better choice for the clinical evaluation of ventricular ectopy.

Acknowledgment

We are indebted to Nancy Houston, RN for supervising the exercise tests, to Cay Fotopolos for recording the exercise tests, to Arlisa Ferrara for computer assistance and to Dorothy Potter for typing the manuscript.

APPENDIX

Computations Related to Reproducibility Of a Two Category Response Test

Test 1 \ Test 2	+	−	
+	9	3	12
−	7	18	25
	16	21	37

N: total sample size = 37

P_1: incidence of a positive test result, test 1 = 12/37 = 0.32

P_2: incidence of a positive test result, test 2 = 16/37 = 0.43

P_0: test-retest agreement = (9 + 18)/37 = 0.73

P_c: chance agreement = $P_1P_2 + (1 - P_1)(1 - P_2)$
= (0.32) (0.43) + (1 − 0.32) (1 − 0.43)
= 0.52

Kappa = $(P_0 - P_c)/(1 - P_c)$ = (0.73 − 0.52)/(1 − 0.52) = 0.44

McNemar test: Prevalence change $(|7 - 3| - 1)^2/7 + 3$ = 0.18

Percent reproducibility of a negative test = 18 × 100/25 = 72%

Percent reproducibility of a positive test = 9 × 100/12 = 75%

Computations Related to Reproducibility of a Three Category Response Test

Test 1 \ Test 2	Absent	Simple	Complex	
Absent	18	5	2	25
Simple	3	5	0	8
Complex	0	1	3	4
	21	11	5	37

N: Total sample size = 37

Incidence	Test 1	Test 2
Absent	25/37 = 0.68	21/37 = 0.57
Simple	8/37 = 0.22	11/37 = 0.30
Complex	4/37 = 0.11	5/37 = 0.14

P_0: Test-retest agreement = (18 + 5 + 3)/37 = 0.70

P_c: Chance agreement = (0.68) (0.57) + (0.22) (0.30) + (0.11) (0.14) = 0.47

Kappa = (0.70 − 0.47)/(1 − 0.47) = 0.44

Percent reproducibility of absent PVC's = (18 × 100)/25 = 72%

Percent reproducibility of simple PVC* = 5/8 = 63%

Percent reproducibility of complex PVC† = 3/4 = 75%

* Simple premature ventricular complexes (PVC): 3 PVC/min or less, isolated premature ventricular complex.

† Complex PVC: 4 PVC/min or greater or bigeminy, couplets or ventricular tachycardia.

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A Case for Norpace (disopyramide phosphate)

Patient: B.P.

Age: 59 Sex: M Race: Cau

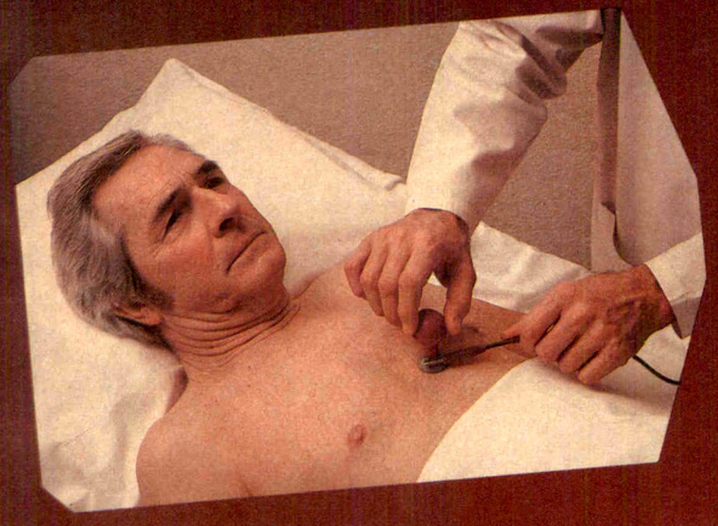
Weight: 175 BP: 130/70

History: MI (date unknown)

Diagnosis: Coronary artery disease, COPD, angina pectoris, paroxysmal ectopic rhythms

Two placebo capsules administered in accord with study protocol.

Trendscriber® recording indicated high frequency of severe ectopic activity, and Norpace loading dose, 300 mg, was given after only 1 hour 11 minutes of placebo period.



For effective control of specific ventricular arrhythmias

Norpace®
(disopyramide phosphate)

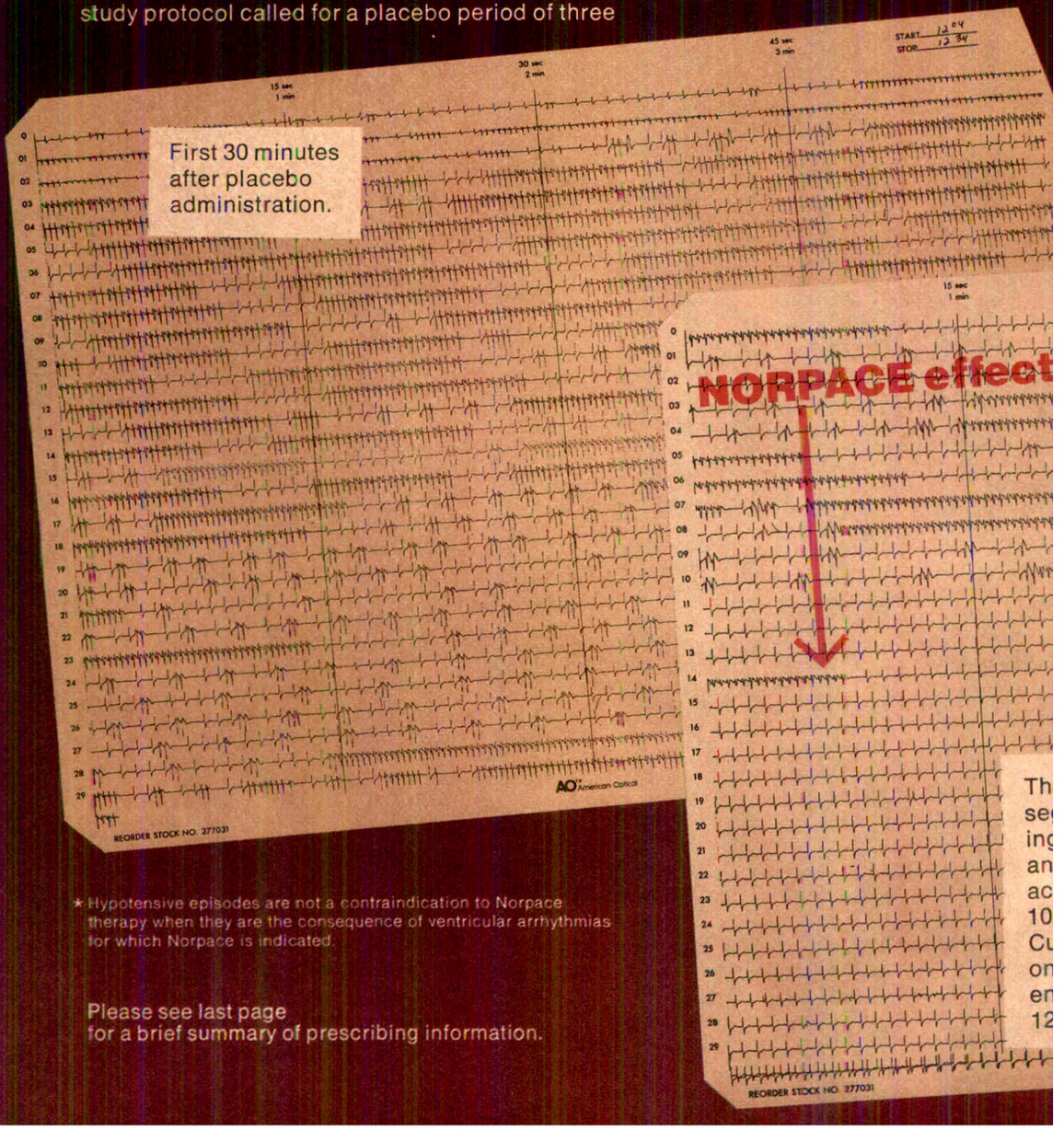
Please see last page
for a brief summary of prescribing information.

In specific ventricular arrhythmias...

Norpace
(disopyramide phosphate)

Case report from oral acute study

This patient, a 59-year-old white male weighing 175 lb, with BP of 130/70 and history of MI of unknown date, was found to have coronary artery disease, chronic obstructive pulmonary disease, angina pectoris and paroxysmal ectopic rhythms. After 71 minutes of placebo period, patient was given a 300-mg loading dose of Norpace (disopyramide phosphate) followed by maintenance doses of 150 mg q 6 h for 72 hours. Although the study protocol called for a placebo period of three hours, the attending physician initiate arrhythmic therapy with Norpace only 11 minutes after placebo administrati the patient was experiencing a hypote episode directly attributable to severe activity.* Objective improvement, as by the adjacent recordings, was visib than two hours after the loading dose was given.



* Hypotensive episodes are not a contraindication to Norpace therapy when they are the consequence of ventricular arrhythmias for which Norpace is indicated.

Please see last page
for a brief summary of prescribing information.

Objective evidence of efficacy

Results obtained in this single case history are typical of the overall results of the complete multicenter study. It is presented to demonstrate the means by which the study data were collected. This study was designed with two objectives: first, to reinforce the previous studies establishing the efficacy and safety of Norpace; second, to determine the time of onset of antiarrhythmic activity.

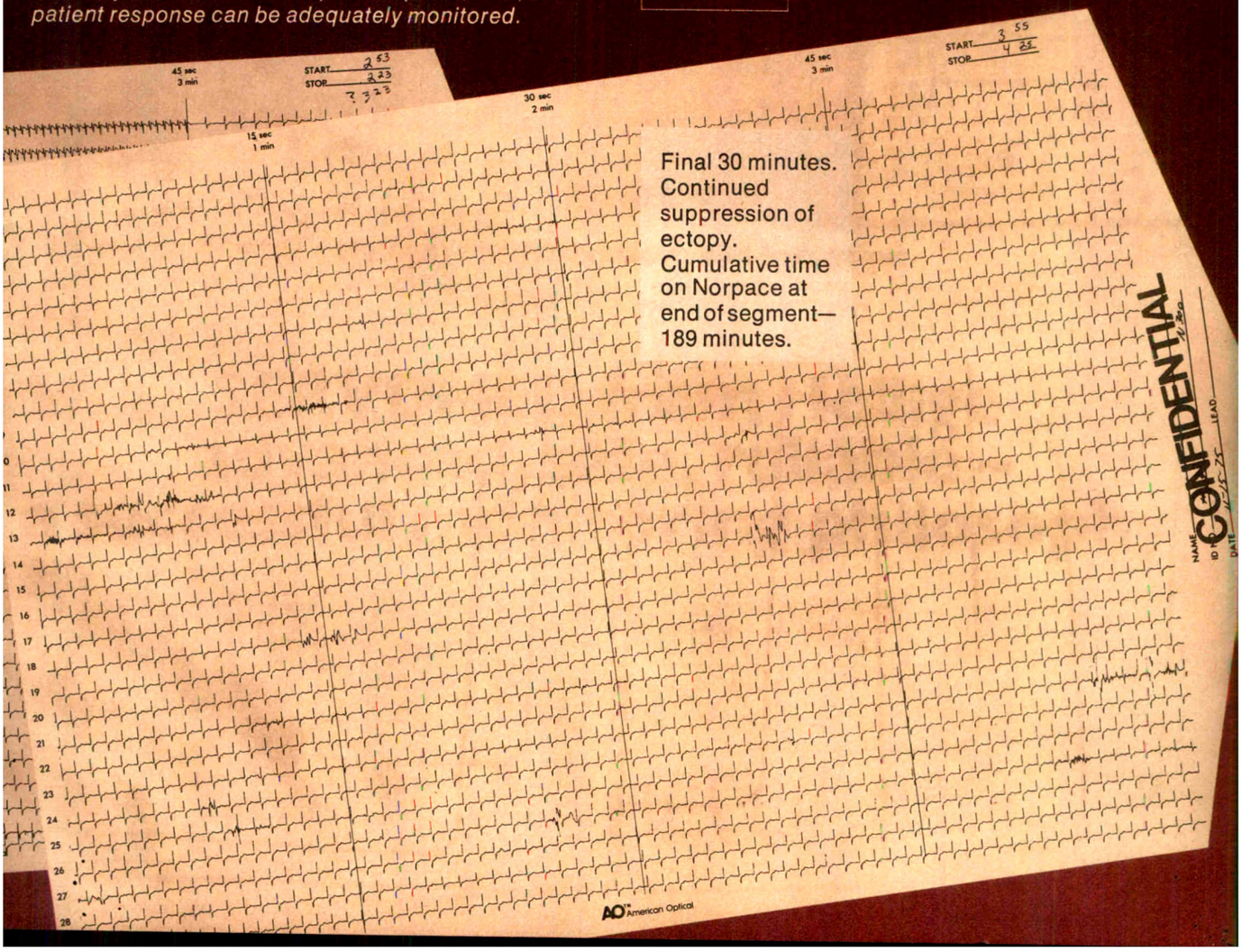
Study protocol required all patients to receive a 300-mg loading dose.

Since patients with arrhythmias are frequently in life-threatening circumstances, a loading dose was used in this study to provide the physician with information that would be useful in critical situations. In practice, a loading dose should ***not*** *be used unless the attending physician has determined that the arrhythmia observed requires rapid control, and patient response can be adequately monitored.*

Effective control of specific ventricular arrhythmias

- Virtually complete suppression of ectopy after 1 hour 53 minutes . . . with no further episodes of ventricular tachycardia
- Continued efficacy over next 72 hours with maintenance dose of 150 mg q 6 h
- Rapid onset of action
- Antiarrhythmic activity sustained by maintenance dose
- Well tolerated
- Norpace (disopyramide phosphate) is a unique therapeutic agent which is indicated for unifocal, multifocal and paired PVCs, and for episodes of ventricular tachycardia

SEARLE



Final 30 minutes. Continued suppression of ectopy. Cumulative time on Norpace at end of segment—189 minutes.

Norpace®
(disopyramide phosphate)
For effective control of specific ventricular arrhythmias

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:

Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In some patients with marginally compensated heart failure, Norpace may worsen cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace.

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *General:* nervousness, dizziness, general fatigue/muscle weakness, headache, malaise. *Cardiovascular:* hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. *Dermatologic:* generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, hypoglycemia, dysuria. Acute psychosis and cholestatic jaundice, both reversible, have been reported.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.

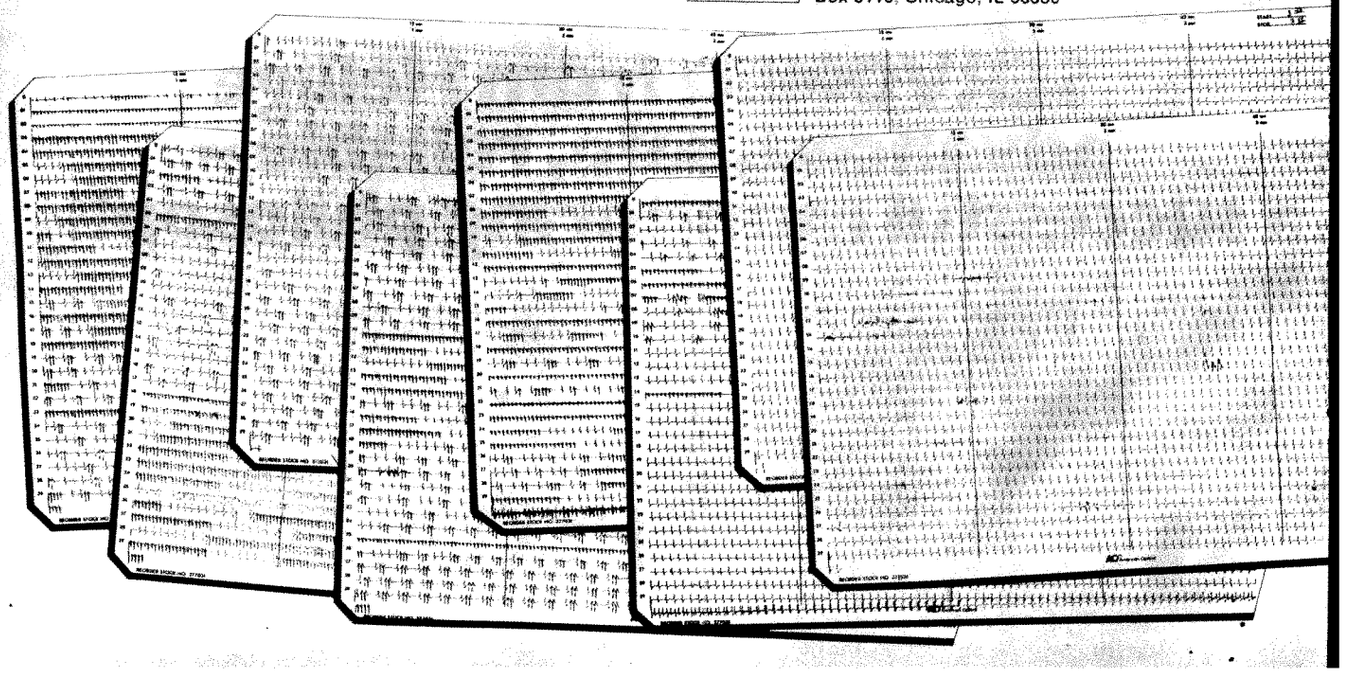
If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

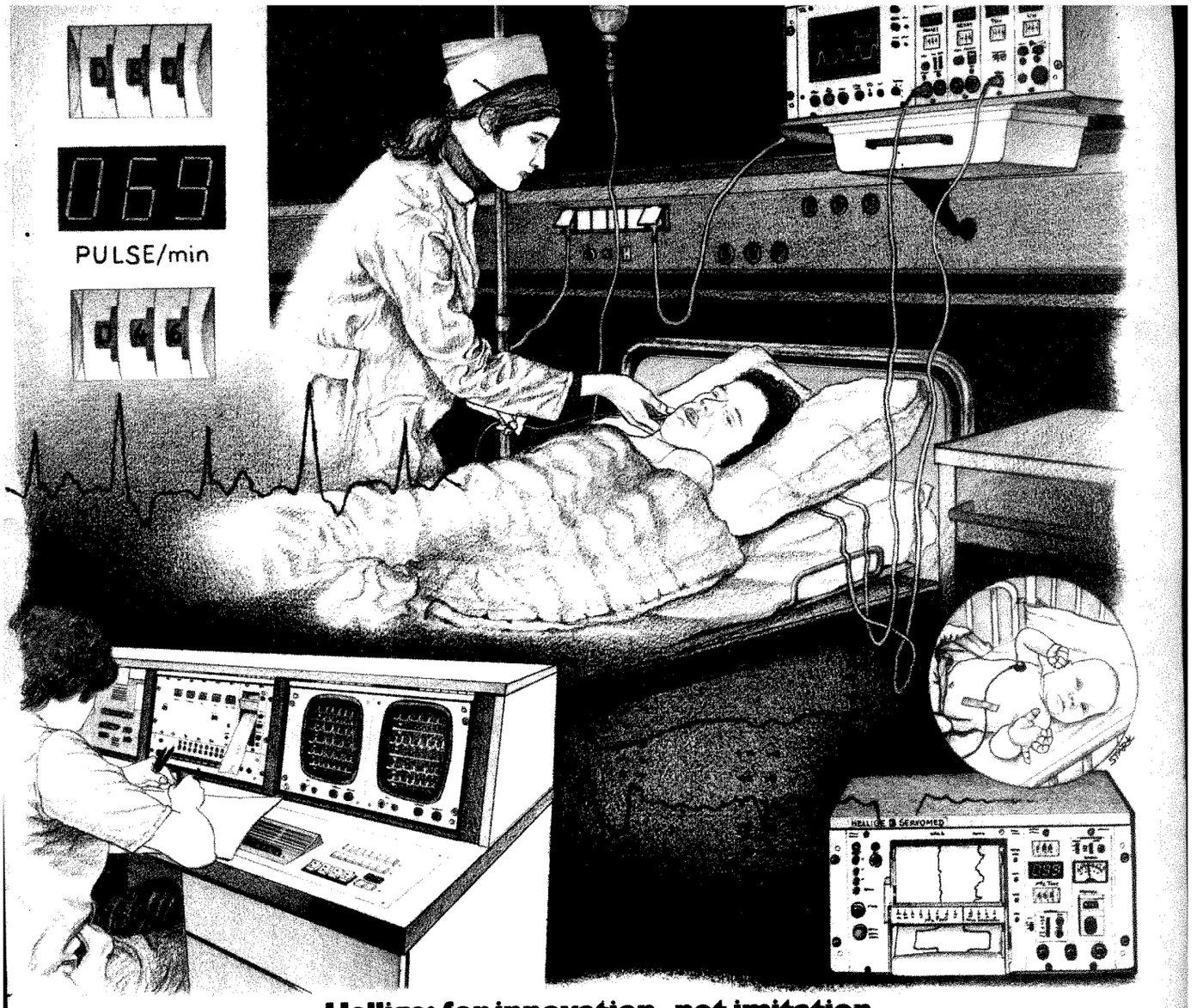
See current complete prescribing information for dosage recommendations.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100 capsules.

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SERVOMED from Hellige advanced, safe, reliable – a successful monitoring philosophy

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CPI'S NEW POROUS TIP LEAD: THE PROBLEM SOLVER

PROBLEM: Endocardial Lead Dislodgement, Causing Threshold Rise or Loss of Capture.

SOLUTION: CPI's New Porous Tip Lead

CPI addressed the problem of lead dislodgement and designed the problem solver: a unique porous electrode. The tip consists of a platinum-iridium screen covering a mesh ball of the same alloy. Optimally-sized fibers give 85-90% porosity so tissue ingrowth knits the tip to the endocardium. Within 24 hours post-implant, the electrode begins its embedment. Clinical studies have demonstrated markedly reduced dislodgement with the porous tip lead. In animal trials, the dislodgement rate was significantly lower than the solid tip control group.[1]

Histologic studies show tissue ingrowth in the acute phase, resulting in a secure electrode-tissue bond chronically, with a noticeably thinner and more structured fibrotic capsule that increases sensing capability.

PROBLEM: An Electrode Tip Must Be Small to Pace Efficiently, but Large Enough to Sense Effectively.

SOLUTION: CPI's New Porous Tip Lead

For pacing the 7.5mm² tip offers reduced current drain, increasing the longevity of constant voltage pulse generators.

For sensing the tip's porosity allows maximum use of the effective sensing area—more than 50mm²—on exterior and interior surfaces. Presence of tissue and fluid within the tip reduces polarization losses. The electrode transmits a larger R-wave, so it offers a sensing advantage.

PROBLEM: Fibrotic Capsule at Lead Tip Can Reduce Chronic Sensing Ability.

SOLUTION: CPI's New Porous Tip Lead

The platinum-iridium mesh fibers are 25μm in diameter, approximating cardiac cell size and thus minimizing tissue reaction.[2] The electrode becomes an integral part of the endocardium. Similar success has been experienced with Dacron fibers of the same size used in artificial heart valves.

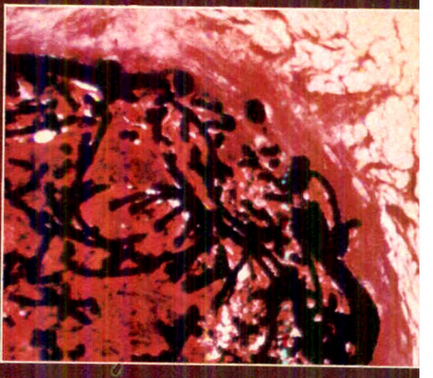
Biocompatible size and quick stabilization mean the electrode causes very little endocardial irritation. Our histologic studies reveal that the fibrotic capsule surrounding the porous tip is significantly thinner than the capsule around a solid tip. The capsule is typically more structured, further indication of this electrode's biocompatibility.

Slimming the fibrotic capsule has significant results—the cardiac signal amplitude and slew rate remain high, so the lead senses reliably in the chronic phase.

Low Dislodgement Rate. Efficient Sensing and Pacing...the Problem Solver from CPI.



Shown 24 hours post-implant, a cross-sectional 100X magnification of the porous tip-canine tissue interface. A fibrinoid collagen capsule has penetrated the outer lattice. Optimally spaced platinum-iridium fibers have allowed electrode ingrowth to begin.



Shown five months post-implant, a cross sectional 100X magnification of the porous tip-canine tissue interface. Dense connective tissue has penetrated the intraelectrode spaces. The fibrotic capsule measures about 300 microns in thickness.

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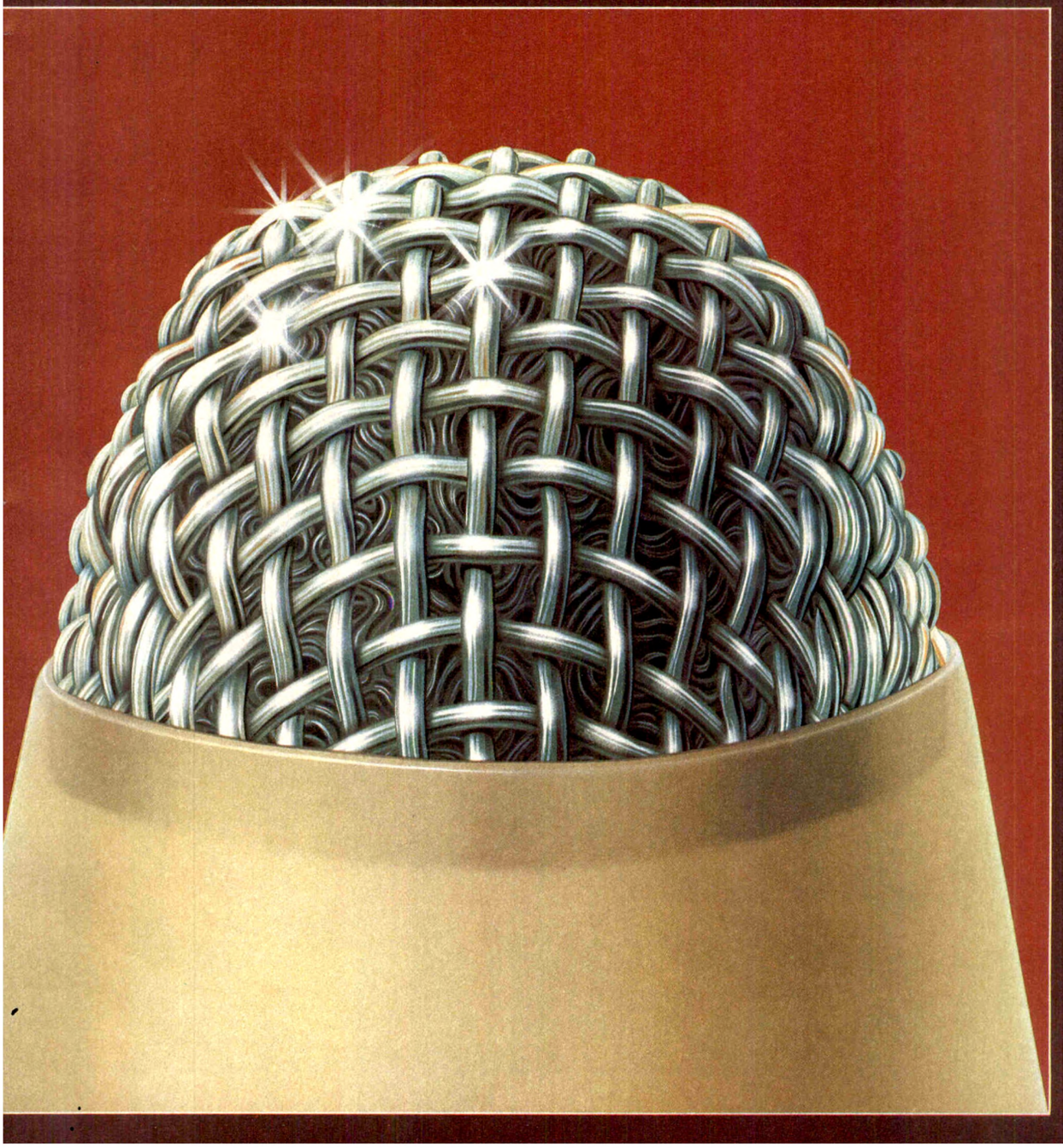
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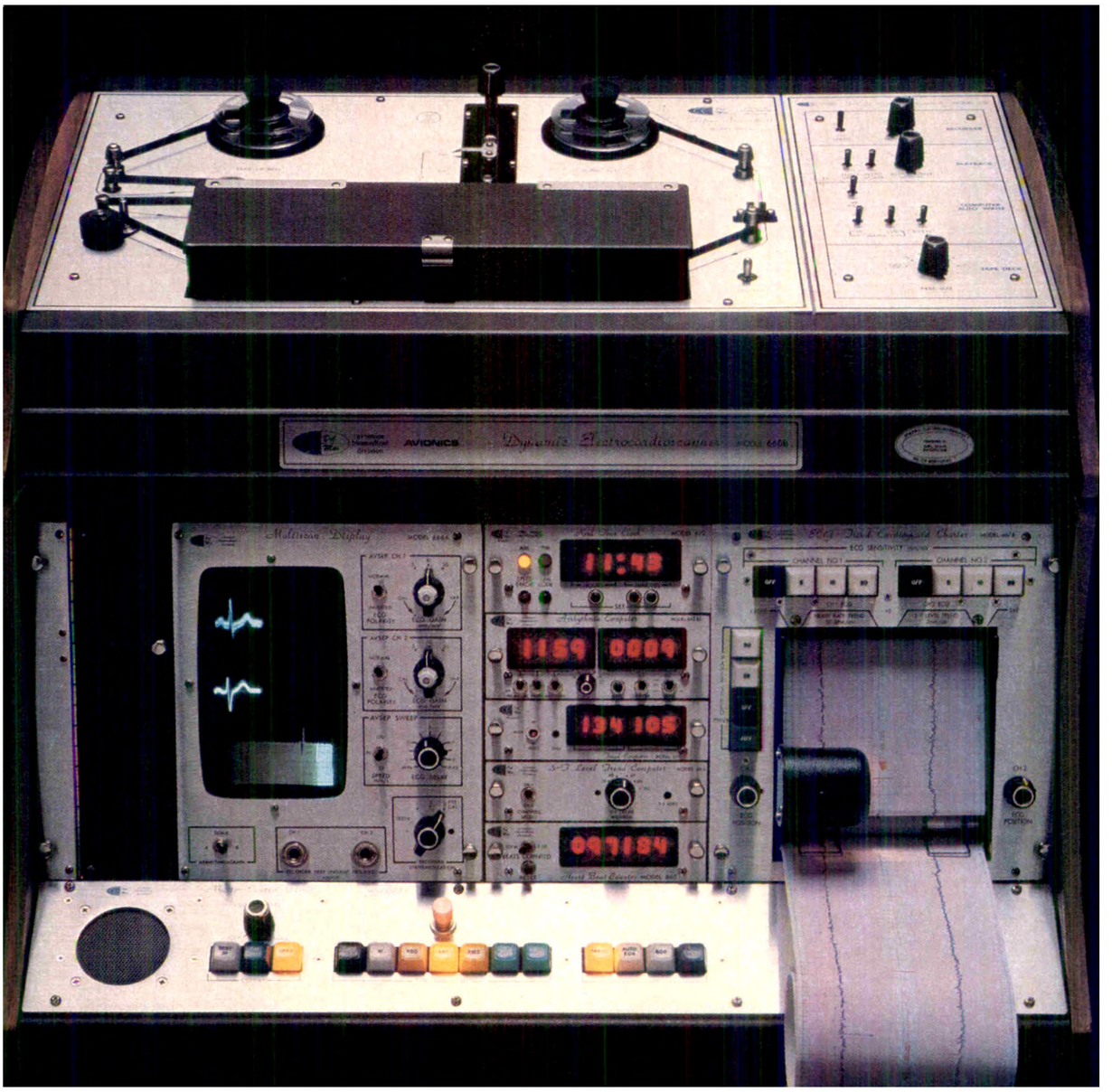
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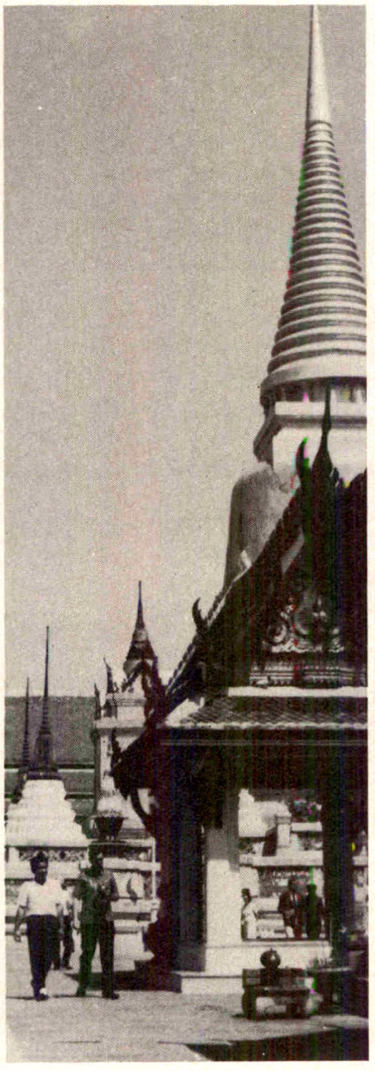
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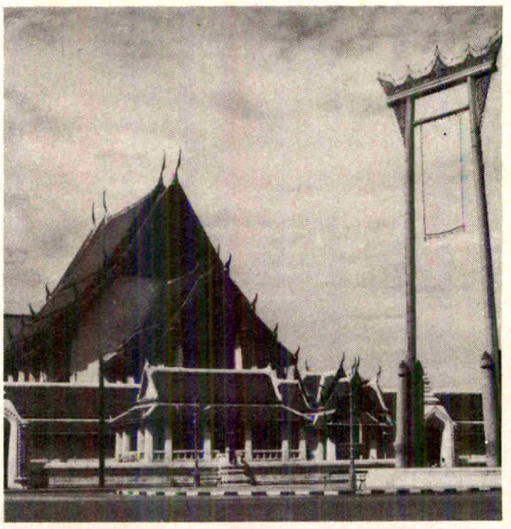
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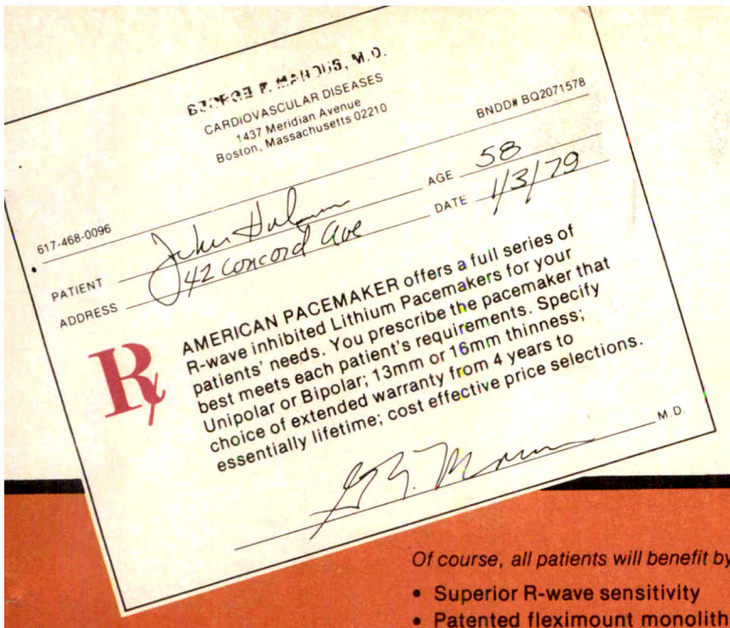








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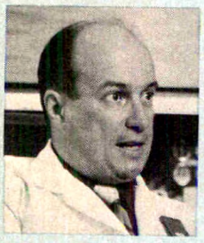


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The interview excerpted here was conducted with Gerald S. Johnston, M.D., Chief of Nuclear Medicine, Clinical Center of the National Institutes of Health, Washington, D.C.

Q. Dr. Johnston, what observations have come from N.I.H. work with multiple gated blood pool studies?

A. The equilibrium method is a much more reliable test than the traditional ECG method. Patients with forms of aortic stenosis, whose resting ejection fractions are higher than normal, experience a drop in ejection fraction during exercise. Following correction of the stenotic lesion, the ejection fraction rises. With exercise there is an improvement in the ejection fraction of patients who have had coronary bypass surgery, indicating that patients can benefit from this operation. Studying patients with aortic insufficiency has provided some hope that the nuclear method may be helpful in selecting the optimal time for valvular replacement.

Q. Comparing multiple gated studies with thallium studies, which in your opinion are easiest to interpret?

A. They are both relatively easy to interpret once the observer has had some experience with them. Because the thallium studies are stationary studies, the subtleties of a very minor lesion might escape you. Because the wall is moving in an equilibrium study, you should be able to pick up very subtle lesions. Therefore, either would be relatively easy to interpret, but probably the equilibrium study would be the easiest.

Q. Which of the two studies yields the most diagnostic information?

A. The equilibrium study gives you more information. The thallium study will show a wall defect if there is an infarct or marked ischemia. However, deficiencies in coronary flow are a bit harder to pick up where myocardial function is still intact. When comparing a rest and exercise equilibrium study, slight abnormalities can be readily observed.

Q. What particular advantages do nuclear cardiology studies have over other methods in the evaluation of heart disease?

A. These procedures are less invasive and provide global and regional functional information. Contrast studies are more invasive. In addition, a significant amount of radiation is required for contrast studies so that repeating them is not taken lightly. Once the initial baseline nuclear cardiology information is obtained from a patient, one would then be in a position to follow the patient's status and see if he was improving as a result of treatment. This is one of the big advantages of these methods, particularly the equilibrium approach.

Q. In your research, how do these tests correlate with cineangiography?

A. We find that the nuclear cardiology data correlates very well with coronary catheterization and contrast angiography data. The three dimensional nuclear data gives us an edge over contrast angiography's two-dimensional view. In all probability, nuclear cardiology studies will become the standard with which to judge contrast angiography.

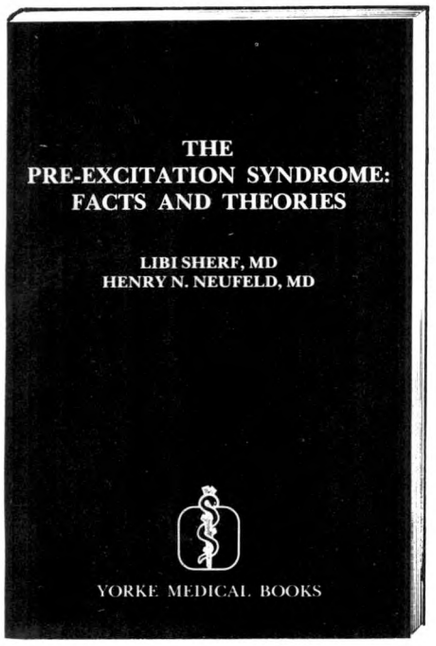
Q. As you look to the future, is nuclear cardiology going to become the primary diagnostic method in cardiac disorders?

A. When you are involved with nuclear cardiology, it seems like that may well be the case. A considerable amount of effort is going into simplifying the computerized aspects of nuclear cardiology as well as improving the detector devices. However, considering the large amount of information gained in exchange for the small dose of radiation that is involved in this method, I think that nuclear cardiology has the potential of being one of the primary methods used in cardiology.

For the complete transcript of this interview with Dr. Johnston, write Inner-View, General Electric Company, Medical Systems Division, P.O. Box 414 (Mail Code W-504), Milwaukee, WI 53201.

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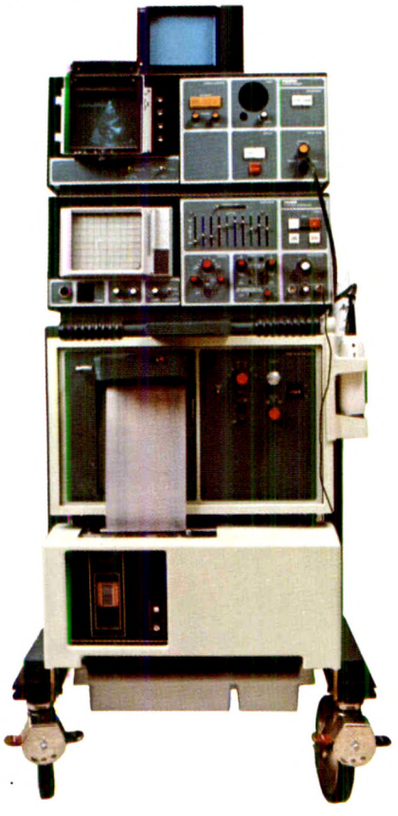
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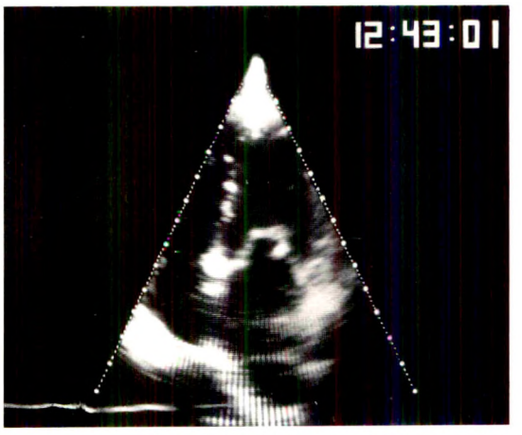
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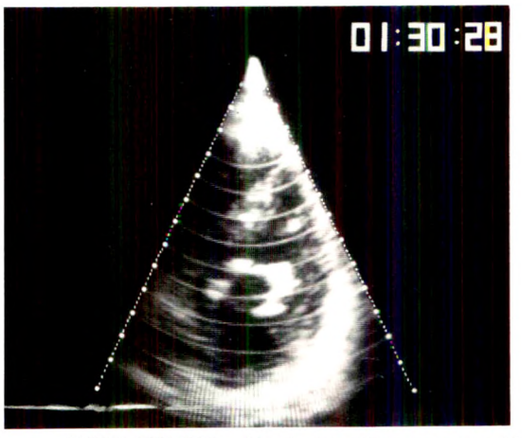
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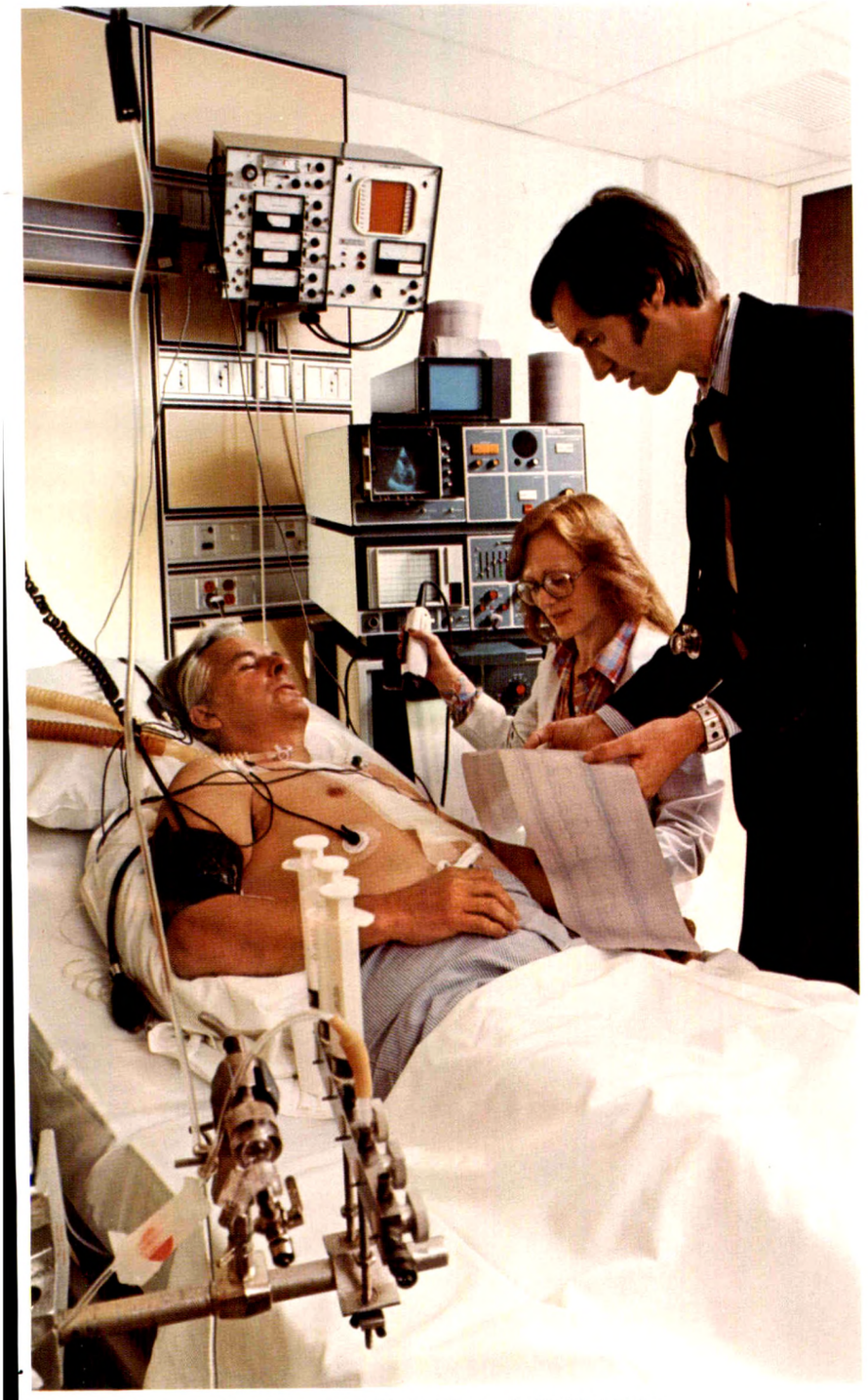


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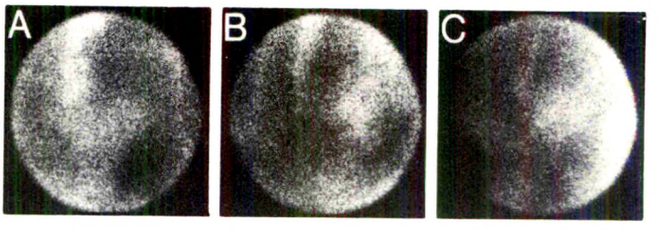
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Prevalence of Diagnostic Abnormalities in Patients With Genetically Transmitted Asymmetric Septal Hypertrophy

FOLKERT J. ten CATE, MD
PAUL G. HUGENHOLTZ, MD, FACC
WIM G. van DORP
JOS ROELANDT, MD, FACC

Rotterdam, The Netherlands

Echocardiographic studies were performed in 100 patients from a general population with cardiac disease and in 33 patients with classic hypertrophic obstructive cardiomyopathy and 116 of their first degree relatives. The findings were compared with those in 35 normal persons. The prevalence rate of asymmetric septal hypertrophy (ventricular septal to free posterior wall ratio greater than 1.3) was 8 percent in the general population with heart disease. No further clinical or echocardiographic evidence was found for a familial disease. The ventricular septal to free posterior wall ratios for this group and the normal subjects had a unimodal distribution curve. All patients with hypertrophic obstructive cardiomyopathy demonstrated asymmetric septal hypertrophy, a decreased systolic septal thickening of less than 25 percent and a characteristic left ventricular shape in the cross-sectional echocardiogram. The ventricular septal to posterior wall ratios in their 116 relatives had a bimodal distribution curve; in 35 relatives the ratio indicated asymmetric septal hypertrophy and in 81 the ratio was normal. In addition, all 35 relatives with echocardiographic evidence of asymmetric septal hypertrophy had decreased systolic septal thickening (less than 25 percent) and in 17 the echocardiographic left ventricular shape was similar to that in patients with hypertrophic obstructive cardiomyopathy. In contrast, the 81 relatives who had no asymmetric septal hypertrophy had normal systolic septal thickening and a normal left ventricular shape. The clinical examination, electrocardiogram and chest X-ray film were less sensitive than the echocardiogram in detecting diagnostic abnormalities in the 35 relatives with asymmetric septal hypertrophy.

It is concluded that echocardiographically assessed asymmetric septal hypertrophy can be considered the anatomic marker for hypertrophic cardiomyopathy only when, in addition, a decreased systolic septal thickening and, to a lesser degree, an abnormal left ventricular shape are present. The asymmetric septal hypertrophy in these cases probably represents the anatomic expression of a genetic defect that has an autosomal dominant pattern of inheritance. In so-called "borderline" cases with echocardiographic signs of an abnormal ventricular septal to posterior wall ratio, a definitive clinical diagnosis of hypertrophic cardiomyopathy could be made only after echocardiographic screening of family members for the presence of asymmetric septal hypertrophy.

From the Department of Clinical Echocardiography at the Thoraxcenter Academic Hospital "Dijkzigt" and Erasmus University Rotterdam, The Netherlands. Manuscript received August 4, 1978; revised manuscript received November 17, 1978, accepted November 21, 1978.

Address for reprints: F. J. ten Cate, MD, Thoraxcenter, P.O. Box 1738, Rotterdam, The Netherlands.

Echocardiographic studies in first degree relatives of patients with proved symptomatic hypertrophic obstructive cardiomyopathy[1] or idiopathic hypertrophic subaortic stenosis[2] have shown that the disease is genetically transmitted.[3,4] In these studies, asymmetric septal hypertrophy detected on echocardiography was used as the anatomic marker to establish the presence of this primarily muscular disorder. However, echocardiographically determined disproportionate septal hypertrophy has been documented in infants with congenital heart

disease[5] and in adults with valvular heart disease[6] with no evidence of hypertrophic cardiomyopathy. Therefore, it seems important to distinguish between asymmetric septal hypertrophy as a primary ("genetic") abnormality and disproportionate septal thickening, which can be present on echocardiography as a secondary phenomenon in response to hemodynamic abnormalities.

Earlier work from this laboratory had indicated that asymmetric septal hypertrophy is a familial disease genetically transmitted by an autosomal dominant trait. We undertook this study to determine whether echocardiographically detected asymmetric septal hypertrophy is indeed a specific disease entity whose findings can be distinguished from those in the general population with heart disease or in apparently normal persons.

Methods

Selection of Patients

Four groups of patients were compared with a group of healthy persons who served as control subjects. The five groups were constituted as follows:

Normal persons: The 35 persons in the control group had no history of heart disease and had normal findings on physical examination, electrocardiogram and posteroanterior chest X-ray film.

General population with heart disease: The 100 patients in the group underwent complete hemodynamic evaluation for diagnosis of cardiac disease. Right and left heart catheterization was followed by single plane left ventriculography (right anterior oblique projection). Twenty-nine patients had coronary artery disease, 18 mitral valve disease, 16 congenital heart disease and 7 minimal heart disease. Fifty-nine were male and 41 female (mean age [± standard error or the mean] 41 ± 15 years).

Hypertrophic obstructive cardiomyopathy: Thirty-three patients (13 male and 20 female; mean age 42 ± 14 years) had hemodynamic (21 patients) and echocardiographic (33 patients) proof of hypertrophic obstructive cardiomyopathy. Diagnosis in the 12 patients who did not undergo cardiac catheterization was based on characteristic clinical findings, family history and electrocardiographic, phonocardiographic and mechanocardiographic findings.

Family members with asymmetric septal hypertrophy: There were 35 first degree relatives of patients with proved hypertrophic obstructive cardiomyopathy (19 male, 16 female; mean age 36 ± 4 years) who had unequivocal echocardiographic evidence of asymmetric septal hypertrophy. These patients were identified when 116 available first degree relatives of patients with proved hypertrophic obstructive cardiomyopathy were screened for presence of the disease on the basis of history, physical examination, electrocardiogram, chest X-ray film and M mode and cross-sectional echocardiograms.

Family members without asymmetric septal hypertrophy: Eighty-one first degree relatives of patients with proved hypertrophic obstructive cardiomyopathy (36 male, 45 female; mean age 28 ± 12 years) underwent the same screening procedure but had no echocardiographic evidence of asymmetric septal hypertrophy.

Echocardiography

Measurements: The echocardiograms were obtained with a commercially available apparatus that included single element and multi-element equipment with real time two dimensional display facilities. The M mode echocardiograms were recorded with a Honeywell linescan recorder (Visicorder 1856) on light-sensitive Kodak linagraph paper. The two dimensional images were registered on videotape through a videorecorder (Sony V-12). During examination the position of the patients was changed until the best resolution of the interventricular septum was obtained. Several M mode scans were recorded, starting with the transducer perpendicular to

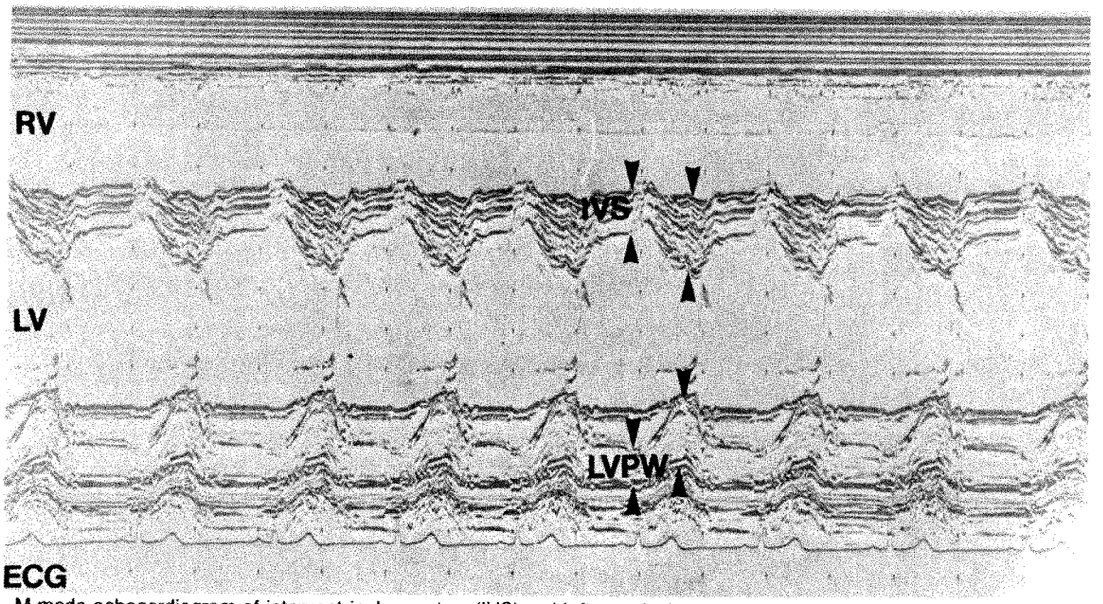


FIGURE 1. M mode echocardiogram of interventricular septum (IVS) and left ventricular posterior wall (LVPW). Measurements for thickness at end-diastole and end-systole are shown (see arrows). For further explanation see text. ECG = electrocardiogram; LV = left ventricle; RV = right ventricle.

the chest wall until the interventricular septum and posterior wall could be clearly identified. Gain settings were continuously adjusted to obtain best visualization of both the interventricular septum and left ventricular posterior wall at a level just beneath the tips of the mitral valve leaflets (Fig. 1).

The thickness of the interventricular septum and the left ventricular posterior wall was measured just after the P wave of the simultaneously recorded electrocardiogram for end-diastole (Td). The largest dimension was taken to represent end-systole (Ts). Fractional thickening of both the interventricular septum and left ventricular posterior wall was calculated as Ts − Td/Td × 100 percent.[7] The two dimensional images were performed in a sagittal plane following the long axis of the left ventricle.[8]

During subsequent analysis, left ventricular shape and the contraction pattern of both the interventricular septum and left ventricular posterior wall (akinetic, normal or hyperkinetic) were described qualitatively. Derived measurements consisted of interventricular septum/left ventricular posterior wall ratio and percent systolic septal thickening. Asymmetric septal hypertrophy was considered present when the septal thickness exceeded the left ventricular posterior wall thickness by 30 percent.[9]

Validity of echocardiographic measurements: Before the study we attempted to determine the validity of the echocardiographic measurements of wall thickness in our laboratory. We studied 23 unselected patients who were referred to our laboratory for a variety of cardiac diagnoses during a 3 month period. To improve detection of the right septal endocardium, which can sometimes be confused with parts of the tricuspid apparatus, 10 cc of saline solution was injected into a peripheral vein (echo contrast agent).[10] Duplicate measurements of septal thickness were made independently by two observers for the echocardiogram with and without the echo contrast agent. This procedure allows determination of the difference between each pair of measurements and calculation of standard deviations (Table I).

The results showed that the standard deviation of the difference between duplicate measurements of the two observers (interobserver variability) was 1.23 and 1.01 mm, respectively, when an echo contrast agent was used, whereas these values were 0.94 and 1.48 mm, respectively, for the duplicate measurements made without a contrast agent. These values are in the range of the axial resolution of ultrasound in human tissue.[8] Therefore it appears that although the use of an echo contrast agent can clarify the diagnosis in some borderline cases, it does not increase the accuracy of septal measurements.

Analysis of data: The Student t test for independent observations was used to determine the statistical significance of differences between measurements.[11] All measurements were carried out in duplicate by two independent observers.

Results

Normal persons and patients from the general population with heart disease: The distribution of the ventricular septal/left ventricular posterior wall ratios of the persons studied are shown in Figures 2 and 3. These ratios present a unimodal distribution curve in the normal subjects and patients from the general population with heart disease, having a mean value of 0.9 ± 0.1 and 1.0 ± 0.1, respectively.

Eight of the 100 patients (8 percent) from the general population with heart disease had a ratio that exceeded 1.3; 3 of these had coronary artery disease, 2 aortic valve disease and 3 congenital heart disease. Of these eight, one patient with coronary artery disease and a true

TABLE I

Results of Duplicate Echocardiographic Measurements of the Interventricular Septum (IVS) by Two Observers With and Without Echo Cardiographic Contrast Agent in 20 Unselected Patients With a Variety of Cardiac Diagnoses

Case no.	IVS Thickness (mm)			
	With Contrast		Without Contrast	
	Observer I	Observer II	Observer I	Observer II
1	10 (11)	10 (10)	11 (11)	11 (11)
2	10 (12)	12 (11)	10 (10)	8 (8)
3	12 (14)	13 (12)	9 (9)	9 (9)
4	12 (12)	11 (12)	10 (10)	8 (8)
5	15 (19)	19 (17)	12 (12)	13 (13)
6	13 (11)	12 (13)	10 (10)	11 (11)
7	16 (15)	17 (16)	14 (14)	16 (16)
8	25 (24)	23 (22)	25 (25)	24 (25)
9	12 (13)	13 (11)	11 (10)	13 (13)
10	10 (10)	11 (11)	11 (12)	12 (12)
11	26 (26)	28 (24)	25 (23)	28 (29)
12	25 (27)	27 (26)	25 (25)	23 (22)
13	11 (11)	11 (11)	11 (12)	12 (11)
14	17 (15)	14 (15)	20 (20)	20 (20)
15	10 (11)	11 (10)	11 (12)	13 (14)
16	14 (14)	15 (15)	15 (16)	14 (15)
17	10 (11)	11 (9)	11 (11)	13 (12)
18	9 (8)	8 (9)	12 (13)	11 (11)
19	10 (12)	13 (10)	11 (11)	13 (12)
20	11 (11)	10 (10)	9 (9)	9 (9)
S	1.23 mm		0.94 mm	
	1.01 mm		1.48 mm	

Figures in parentheses indicate duplicate measurement.
S = standard deviation of differences.

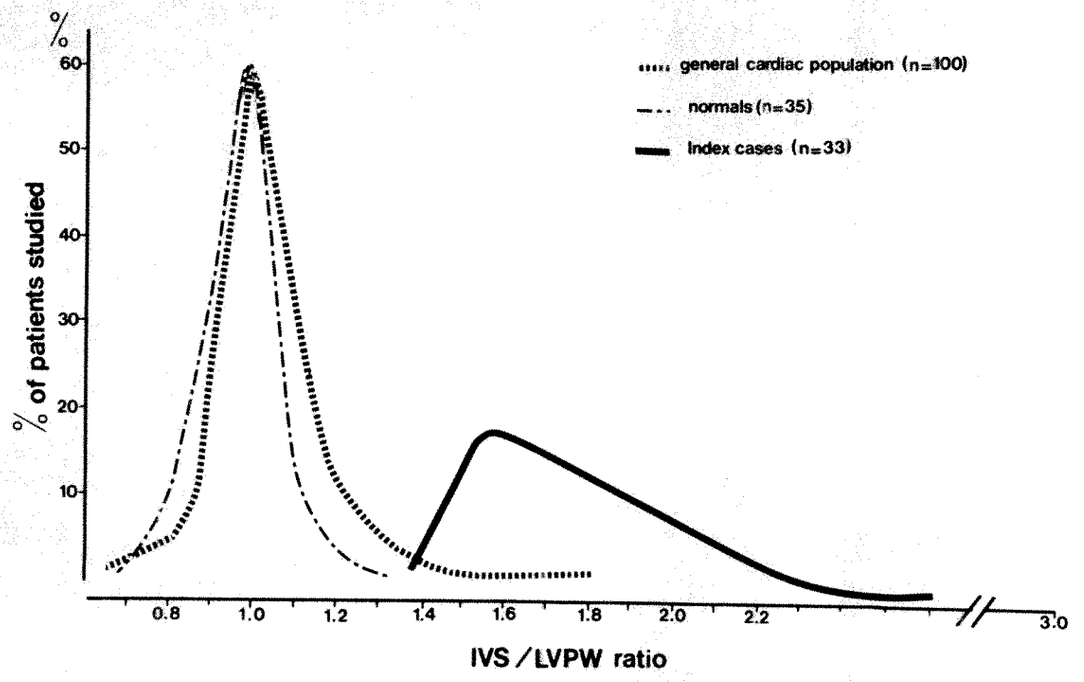


FIGURE 2. Distribution of interventricular septum/left ventricular posterior wall (IVS/LVPW) thickness ratios in 100 patients from the general population with heart disease, 35 normal persons and 33 patients with hypertrophic cardiomyopathy (index cases). Slight overlap exists between the general population with heart disease and the index cases, but separation between those groups is evident when IVS/LVPW ratios are considered. The normal persons have the same distribution of IVS/LVPW ratios as the general population with heart disease. n = number of subjects.

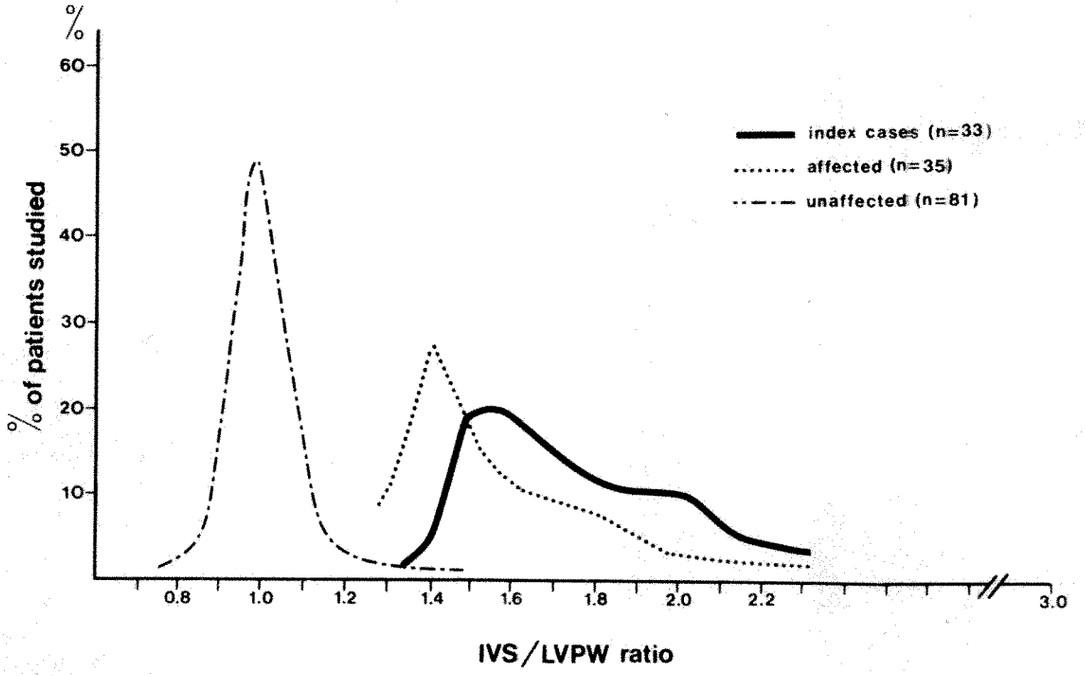


FIGURE 3. Distribution of interventricular septum/left ventricular posterior wall (IVS/LVPW) thickness ratios from 33 patients with hypertrophic obstructive cardiomyopathy (index cases), 35 first degree relatives with asymmetric septal hypertrophy (affected) and 81 first degree relatives without echocardiographic evidence of asymmetric septal hypertrophy (unaffected). This last group can clearly be separated from patients with hypertrophic obstructive cardiomyopathy and their relatives with asymmetric septal hypertrophy. Therefore, the first degree relatives of patients with hypertrophic cardiomyopathy represent a bimodal distribution curve of IVS/LVPW ratios.

posterior wall infarction had a ratio of 1.6, and another with a ventricular septal defect and infundibular pulmonary stenosis had a ratio of 1.8. Neither patient had evidence of a primary cardiomyopathy on family history or other study. The remaining six patients had ratios between 1.3 and 1.6. Patients with hypertrophic obstructive cardiomyopathy can clearly be distinguished on the basis of these ratios from normal subjects and patients from the general population with heart disease.

Patients with hypertrophic obstructive cardiomyopathy and their relatives: The ratios in these patients and their family members showed a bimodal distribution curve of persons with asymmetric septal hypertrophy (33 patients with hypertrophic cardiomyopathy and their 35 family members with echocardiographic signs of asymmetric septal hypertrophy. The ventricular septal/left ventricular posterior wall ratio in the 81 relatives without echocardiographic evidence of asymmetric septal hypertrophy did not differ from values in the control group or in the general population with heart disease.

Because the aim of our study was to describe the clinical and echocardiographic findings in patients with asymmetric septal hypertrophy and their family members, we restricted the clinical analysis of pertinent data to these persons. For these groups, detailed data on history, symptoms and signs, electrocardiograms and chest X-ray films are given in Table II. Table III provides a detailed description of echocardiographic measurements. The data indicate that most family members with asymmetric septal hypertrophy have the same echocardiographic characteristics as patients with hypertrophic obstructive cardiomyopathy. At the time of our study, the first degree relatives without asymmetric septal hypertrophy were classified as normal subjects.

Analysis of genetic transmission of asymmetric septal hypertrophy: For the 33 patients with hypertrophic obstructive cardiomyopathy, representing 33 families, 116 first degree relatives were available for study. In 14 families, no other person with echocardiographic asymmetric septal hypertrophy was found. However, asymmetric septal hypertrophy was documented in two patients by the necropsy data of deceased family members. Pedigree charts were made (Fig. 4) of the 21 families with evidence of genetic transmission of asymmetric septal hypertrophy. The results show a horizontal distribution (relation between siblings) present in 58 percent, a vertical distribution (parent-sibling relation) in 42 percent and both kinds of distribution in 38 percent. These findings are in agreement with the view that the defect is inherited as an autosomal dominant trait.[12]

TABLE II

Characteristics of Subjects With Asymmetric Septal Hypertrophy

	Patients With HOCM (index cases)	First Degree Relatives	
		With ASH	Without ASH
	(33 patients)	(35 subjects)	(81 subjects)
A. History, Signs and Symptoms			
Family history positive for cardiomyopathy	21	35	81
No clinical abnormality	0	15	81
Systolic murmur	32	10	0
Congestive heart failure	5	0	0
Syncope	2	0	0
Arrhythmias	10	3	0
Palpitations and dyspnea	22	6	0
Anginal complaints	14	10	0
Taking medication	33	2	0
B. Electrocardiographic Findings			
No significant abnormalities	0	6	81
Abnormal Q waves	16	9	0
Left ventricular hypertrophy	5	8	0
Right ventricular hypertrophy	3	0	0
T wave abnormalities	20	11	0
Intraventricular conduction abnormalities	3	0	0
Preexcitation syndrome	1	0	0
Supraventricular rhythm disturbances	3	1	0
Ventricular rhythm disturbances	10	0	0
C. Chest X-ray Findings			
Normal findings	2	21	40*
Cardiothoracic ratio >50%	31	14	0
Lung changes due to left heart failure	8	0	0

* In first degree relatives without asymmetric septal hypertrophy, chest X-ray films were not made routinely in children younger than 15 years.

ASH = asymmetric septal hypertrophy; HOCM = hypertrophic obstructive cardiomyopathy.

Discussion

Asymmetric septal hypertrophy as a separate disease entity: Our results indicate that an abnormal interventricular septum/left ventricular posterior wall ratio greater than 1.3 can occur in patients with a variety of acquired or congenital heart diseases. The question arises whether this abnormality is secondary to the underlying cardiac disorder or a manifestation of a coexistent and etiologically separate disease and, more specifically, genetically transmitted asymmetric septal hypertrophy.[3] Our findings suggest that in patients with acquired or congenital cardiac diseases an abnormal interventricular septum/left ventricular posterior wall ratio is not a manifestation of genetically transmitted asymmetric septal hypertrophy.

This conclusion is based on the unimodal distribution curve found in the normal group and in the general population with heart disease and on the negative family history for the presence of genetically transmitted heart disease in eight patients from the general population with heart disease who had an interventricular septum/left ventricular posterior wall ratio greater than 1.3. This finding is in contrast with the apparent bimodal distribution curve found in the population of first degree relatives of patients with symptomatic hypertrophic obstructive cardiomyopathy,

TABLE III

Pertinent Echocardiographic Findings in Family Members of 33 Patients With Hypertrophic Obstructive Cardiomyopathy

	Normal Values*	Patients With HOCM (index cases) (33 patients)	First Degree Relatives	
			With ASH (35 subjects)	Without ASH (50 subjects)
IVS thickness (mm)	8–13	24 ± 6†	19 ± 2†	11 ± 2
LVPW thickness (mm)	8–13	12 ± 3	11 ± 2	11 ± 2
IVS/LVPW thickness ratio (mean end range)	. . .	2.2 (1.4–2.8)	1.7 (1.3–2.3)	1.0 (0.9–1.2)
Systolic thickening of IVS (%)	42 ± 8	9 ± 6†	12 ± 12†	50 ± 11
Systolic thickening of LVPW (%)	52 ± 9	66 ± 30	60 ± 15	70 ± 12
LV shape	Ellipsoid	Banana shape	Banana shape	Ellipsoid

* For this laboratory.
† Statistically different from values in normal control group ($P < 0.005$).
Values are expressed as mean ± standard error of the mean. Figures in parentheses indicate the range of values.
ASH = asymmetric septal hypertrophy; HOCM = hypertrophic obstructive cardiomyopathy; IVS = interventricular septal wall; LV = left ventricular; LVPW = left ventricular posterior wall.

most of whom had a positive family history for cardiomyopathy. However, because we did not separately examine the prevalence of abnormal septum/posterior wall ratio in coronary artery disease, we cannot definitely exclude using echocardiographic criteria alone the combined occurrence of asymmetric septal hypertrophy and coronary artery disease.

Is asymmetric septal hypertrophy a familial cardiomyopathy?: Symptomatic patients with hypertrophic obstructive cardiomyopathy or idiopathic hypertrophic subaortic stenosis have a myopathic disease. The characteristic signs for this disorder, as evaluated in our laboratory, are decreased systolic thickening or contraction of the interventricular septum[7] and an abnormal left ventricular cavity shape as assessed from cross-sectional images. The question is whether these abnormalities are also present in first degree relatives with an abnormal interventricular septum/left ventricular posterior wall ratio. The results of our study indicate that 35 of 116 first degree relatives of patients with hypertrophic cardiomyopathy did have decreased systolic thickening of the interventricular septum. Only 17 had an abnormal left ventricular shape.

We conclude that patients with symptomatic hypertrophic obstructive cardiomyopathy and their affected family members have the same echocardiographic characteristics but different clinical signs and symptoms. Thus, these echocardiographic signs allow the diagnosis of a genetically transmitted cardiomyopathy manifesting with a wide variety of clinical signs and symptoms.

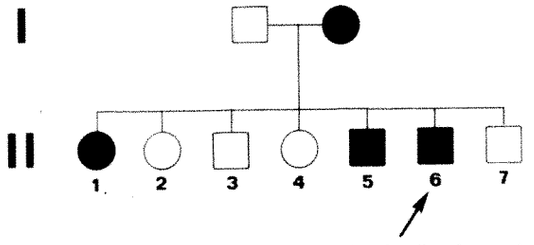


FIGURE 4. Pedigree chart of a representative family of a proband with hypertrophic cardiomyopathy (**arrow**). The echocardiographic study in this family revealed two other siblings with asymmetric septal hypertrophy (1 and 5) and one parent with asymmetric septal hypertrophy. This pedigree chart is in agreement with an autosomal dominant mode of transmission.

Clinical implications: How can genetically transmitted asymmetric septal hypertrophy be excluded as a cause of an abnormal interventricular septum/left ventricular wall ratio in the otherwise asymptomatic person and in patients with congenital or acquired heart disease who have an interventricular septum/left ventricular posterior wall ratio exceeding 1.3? A practical and reliable way to make such a distinction is to examine first degree relatives for asymmetric septal hypertrophy and for decreased septal thickening on echocardiography.

Although histologic examination after biopsy of cardiac septal muscle for the presence of disorganized cardiac cells or extensive hemodynamic and angiocardiographic studies, or both, may provide the absolute evidence, these techniques are not readily applicable or indicated in most clinical situations.[6] Currently, the echocardiographic technique is the most realistic approach.

Echocardiographic limitations: Accuracy in detecting asymmetric septal hypertrophy requires a carefully executed echocardiographic examination technique. Even then, it is sometimes difficult to define accurately the right-sided endocardial echo of the interventricular septum. A better definition of the right-sided septal structures will be realized with the injection of echo contrast agents (5 percent dextrose in water or saline solution) into a peripheral vein.[10]

This study indicates a clinical spectrum ranging from absence of symptoms to the typical findings of hypertrophic obstructive cardiomyopathy or idiopathic hypertrophic subaortic stenosis. All affected persons have the same characteristic echocardiographic features. Asymmetric septal hypertrophy can be considered the anatomic expression of a genetic defect that is transmitted as an autosomal dominant trait.

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Comparison of Two-Dimensional and M-Mode Echocardiography In the Evaluation of Patients With Infective Endocarditis

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M-mode and two-dimensional echocardiographic evaluation of infectious endocarditis and its complications was reviewed. In 21 consecutive patients with clinical endocarditis, 22 valves were involved (12 aortic, 5 mitral and 5 tricuspid). M-mode echocardiography detected vegetations in 10 patients (four aortic, two mitral and four tricuspid) and detected complications of endocarditis in 2 patients (one aortic root abscess and one flail aortic cusp). Two-dimensional echocardiography detected vegetations in 9 patients (four aortic, one mitral and four tricuspid) and detected complications in ten patients (five flail aortic cusps, one aortic root abscess, one sinus of Valsalva aneurysm, two flail mitral leaflets and one flail tricuspid valve). Thus, although M-mode and two-dimensional echocardiography had a similar ability to detect actual vegetations, two-dimensional echocardiography was superior to M-mode echocardiography in diagnosing complications of the destructive process.

M-mode echocardiography is useful in diagnosing valvular vegetations and in detecting some of the complications of bacterial endocarditis.[1] However, it was suggested that M-mode echocardiography will detect vegetations in only approximately 34 percent[2] to 55 percent[3] of patients with bacterial endocarditis. Two explanations for this low sensitivity are possible. First, the diagnostic ability of this technique may be related to vegetation size, and thus M-mode echocardiography may detect only large vegetations. Second, the M-mode technique only visualizes limited areas of the valvular and anular surfaces.

Two-dimensional echocardiography is a technique that provides information about the spatial orientation and motion of intracardiac surfaces that are "silent" to M-mode echocardiography. The purpose of this report is to determine the value of two-dimensional echocardiography in the diagnosis of infective endocarditis and its complications.

Methods

Patients: The M-mode and two-dimensional echocardiographic findings in 21 consecutive patients with a clinical diagnosis of infective endocarditis were reviewed. All 21 patients were febrile. Twelve patients presented with or developed congestive failure during their hospital stay. All had new regurgitant murmurs of the involved valves. Blood cultures were positive in 18 patients (Table I). Three other patients had culture-negative endocarditis; all three had had antibiotic therapy.

Echocardiography: *M-mode echocardiographic studies* were performed in the supine or left lateral decubitus position using a Smith Kline Ekoline 20A ultrasonoscope with a 2.25 megahertz medium (7.5 cm) internally focused transducer. Permanent recordings were obtained with an Irex 101 Continutrace Recorder.

Two-dimensional echocardiographic studies were performed using either a Grumman Health Systems RT-400 or a Varian V-3000 phased-array sector

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scanner. The illustrations presented here were photographed from single frame videotape images. The limitations of such illustrations include (1) a loss of the visual integration of motion that normally accompanies real-time imaging, and (2) a degradation of image quality caused by photographing a single field of a complete videotape frame that normally consists of two interlaced fields. Complete two-dimensional echocardiographic studies included (1) the long axis view to evaluate the aorta, the aortic valve and the mitral valve, (2) transverse views through the aortic and mitral valves, (3) a sagittal view of the tricuspid valve, and (4) the apical view to evaluate the mitral and tricuspid valves.

Surgical or pathologic confirmation was available in 11 patients. Ten patients had successful valve replacement; one patient died before surgery.

Statistical analysis was performed with the chi-square method.

Results

Aortic valve endocarditis: Twelve patients had a clinical diagnosis of aortic valve endocarditis. The M-mode echocardiographic findings in these patients are listed in Table I. Four patients (Cases 3, 4, 6 and 7) had an aortic valve vegetation (Fig. 1). In two patients (Cases 2 and 5) the aortic valve appeared sclerotic, the leaflets were thickened, and leaflet motion was reduced; however, no distinct vegetation was seen. In one patient (Case 8) the posterior aortic wall had a double density, suggesting an aortic root abscess. In five patients (Cases 1, 9, 10, 11 and 12) the aorta and aortic valve were normal.

The two-dimensional echocardiographic findings in the 12 patients with aortic valve endocarditis are also listed in Table I. In four patients (Cases 3, 4, 6 and 7) aortic valve vegetations were identified as rapidly moving high density masses attached to one of the aortic valve cusps (Fig. 2). In four patients the two-dimensional study detected a flail aortic valve cusp (Fig. 3); the M-mode echocardiogram was normal in three of these patients (Cases 1, 9 and 12) and also showed a flail cusp in one of them (Case 3). In addition, one patient (Case 7) whose initial study showed a vegetation later had a flail aortic valve cusp. One patient (Case 2) had a thickened, calcified aortic valve without a distinct vegetation or any other evidence of endocarditis. One patient (Case 8) had a double density of the posterior aortic wall, suggesting an aortic root abscess. One patient (Case 5) had an outpouching of the aorta into the right atrium, suggesting a ruptured sinus of Valsalva aneurysm (Fig. 4). The results of the studies were nor-

TABLE I

Bacteriologic, M-mode and Two-dimensional Echocardiographic and Pathologic Data in 18 Patients with Infective Endocarditis

Patient	Organism	M-Mode Findings	Two-Dimensional Findings	Pathologic Data
		Aortic Valve Endocarditis		
1	Pneumococcus	Normal	Flail cusp	Not available
2	Staph. aureus	Valve sclerosis	Valve sclerosis	Not available
3	Pneumococcus	Vegetation, flail cusp	Vegetation, flail cusp	Vegetation, flail cusp‡
4	Strep. viridans	Vegetation	Vegetation	Vegetation‡
5	Culture negative	Valve sclerosis	Sinus of Valsalva aneurysm	Sinus of Valsalva aneurysm, endocarditis‡
6	Group D Strep.	Vegetation	Vegetation	Vegetation‡
7*a	H. parainfluenza	Vegetation	Vegetation	. . .
b	. . .	Flail cusp	Flail cusp	Flail cusp‡
8	Group A Strep.	Root abscess	Root abscess	Root abscess§
9	Strep. viridans	Normal	Flail cusp	Flail cusp‡
10	Strep. viridans	Normal	Normal	Not available
11	Staph. aureus	Normal	Normal	Not available
12	Strep. viridans	Normal	Flail cusp	Not available
		Mitral Valve Endocarditis		
13	Strep. viridans	Prolapse, vegetation	Prolapse	Not available
14†	Staph. aureus	Normal	Ruptured chordae	Ruptured chordae, endocarditis‡
15	Culture negative	Prolapse	Ruptured chordae	Ruptured chordae, endocarditis‡
16	Strep. viridans	Vegetation	Vegetation	Not available
17	Culture negative	Normal	Normal	Not available
		Tricuspid Valve Endocarditis		
14†	Staph. aureus	Excessive systolic separation	Ruptured chordae	Ruptured chordae, endocarditis‡
18*a	Anaerobic gram negative bacillus	Vegetation	Vegetation	. . .
b	. . .	Normal	Vegetation	Not available
19	Multiple organisms	Vegetation	Vegetation	Vegetation‡
20	Eichinella coodens	Vegetation	Vegetation	Not available
21	Staph. aureus	Vegetation	Vegetation	Not available

* Patients 7 and 18 each had two studies: an initial study (a) and a follow-up study (b). † One patient had both mitral and tricuspid endocarditis. ‡ Surgical findings. § Autopsy findings.
H. = Hemophilus; Staph. = Staphylococcus; Strep. = Streptococcus.

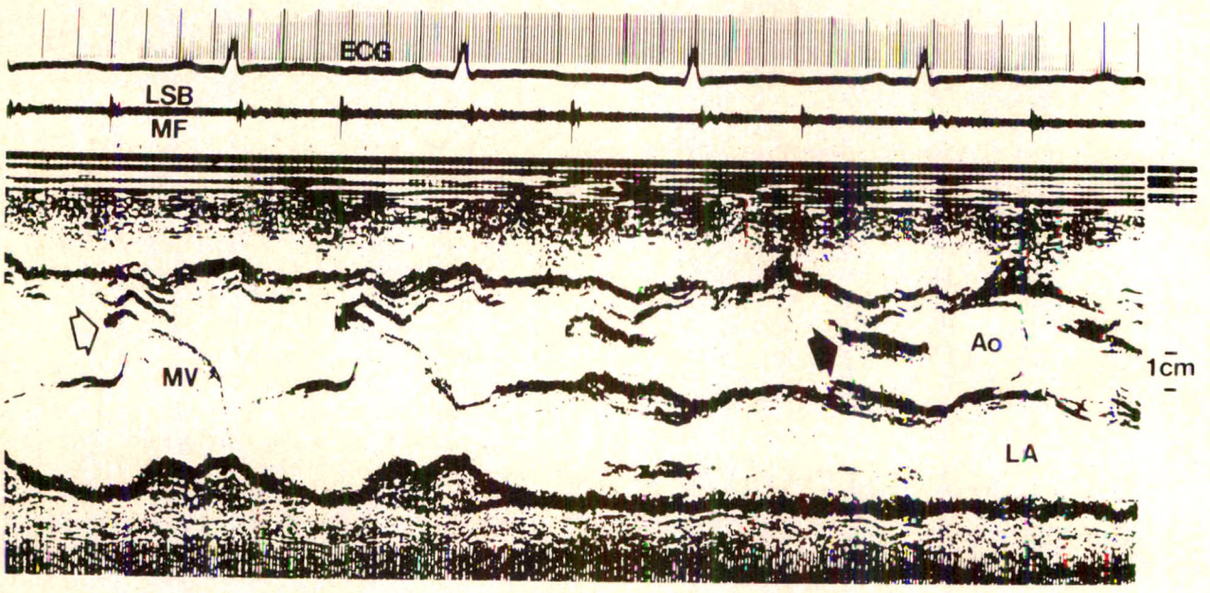


FIGURE 1. Case 7. M-mode echocardiogram in a patient with aortic valve endocarditis. The vegetation (**dark arrow**) is attached to the aortic valve during diastole and also prolapses into the left ventricular outflow tract during diastole (**open arrow**). Ao = aorta; ECG = electrocardiogram; LA = left atrium; LSB MF = left sternal border medium frequency phonocardiogram; MV = mitral valve.

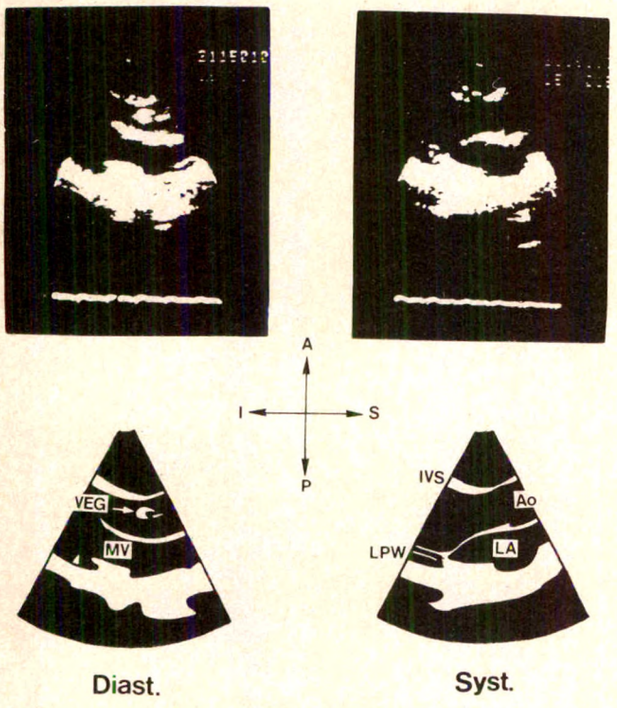


FIGURE 2. Case 7. Diastolic (Diast.) and systolic (Syst.) frames of a two-dimensional echocardiographic study from the same patient with aortic valve endocarditis. Each frame is accompanied by a labeled, idealized diagram. During diastole, the vegetation (VEG) is attached to the aortic valve. During systole, the valve motion is unrestricted, and the vegetation is no longer seen. The study immediately before surgery only showed a flail cusp. The presence of a flail cusp without a vegetation was confirmed at surgery. A = anterior; Ao = aorta; I = inferior; IVS = interventricular septum; LA = left atrium; LPW = left ventricular posterior wall; MV = mitral valve; P = posterior; S = superior.

mal in two patients (Cases 10 and 11). The long axis view was best for detecting a vegetation, flail cusp or root abscess. The transverse view of the aortic valve was useful in detecting a sinus of Valsalva aneurysm.

Anatomic confirmation of these findings was available in seven patients (Table I); three (Cases 3, 4 and 6) had vegetations (one with a flail cusp), one (Case 8) had an aortic root abscess, two (Cases 7 and 9) had a flail cusp without a vegetation, and one (Case 5) had a ruptured sinus of Valsalva aneurysm.

Mitral valve endocarditis: *The M-mode echocardiographic findings* in five patients with mitral valve endocarditis are listed in Table I. Two patients (Cases 13 and 15) had mitral valve prolapse with redundancy and thickening of the anterior or posterior leaflet (Fig. 5). One patient (Case 16) had a vegetation. The M-mode studies in the other two patients (Cases 14 and 17) were normal.

The two-dimensional echocardiographic findings in these patients are listed in Table I. Two patients (Cases 14 and 15) had a flail anterior mitral leaflet (Fig. 6); there was rapid systolic motion of the leaflet's tip beyond the line of mitral valve closure into the left atrium. One (Case 15) of these two patients also had a localized increased anterior mitral valve leaflet thickness. One patient (Case 13) had mitral valve prolapse. One patient (Case 16) had an anterior mitral leaflet vegetation; during systole the vegetation curled into the left ventricular outflow tract. The results of one study (Case 17) were normal. The long axis view was best for detecting a vegetation or a flail valve.

Surgical observation in two patients confirmed the presence of endocarditis with ruptured chordae tendineae.

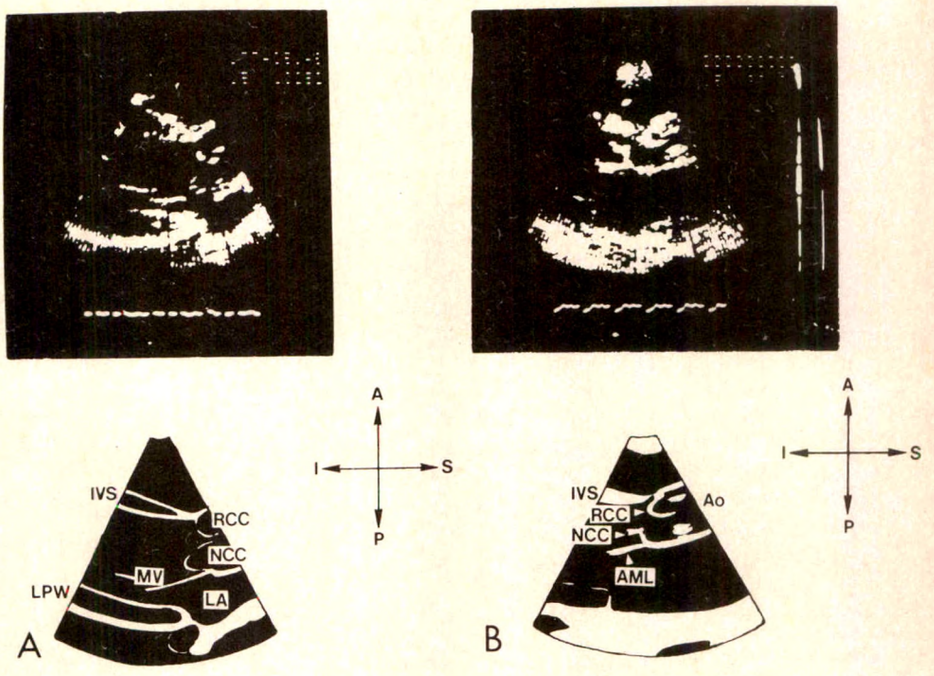


FIGURE 3. Diastolic frames from two-dimensional studies of two patients with aortic valve endocarditis and flail aortic valve leaflets. Each single frame is accompanied by a labeled, idealized diagram. **Panel A,** Case 9. This patient had a flail noncoronary cusp (NCC) without a vegetation confirmed at surgery. The organism was Streptococcus viridans. The M-mode echocardiographic findings were normal. Note that the noncoronary cusp hangs below the right coronary cusp (RCC) into the left ventricular outflow tract. **Panel B,** Case 3. In this patient both a vegetation and a flail noncoronary cusp were confirmed at surgery. The organism was Pneumococcus. The M-mode echocardiogram showed a vegetation prolapsing into the left ventricular outflow tract. Note that the flail noncoronary cusp with an attached vegetation hangs below the right coronary cusp into the left ventricular outflow tract. AML = anterior mitral valve leaflet; other abbreviations as in Figure 2.

Tricuspid valve endocarditis: *The M-mode echocardiographic findings* in five patients with tricuspid valve endocarditis are summarized in Table I. (One patient [Case 14] had both tricuspid valve and mitral valve endocarditis.) In four patients (Cases 18–21) a vegetation was identified (Fig. 7). In the fifth patient (Case 14) the M-mode study disclosed excessive systolic tricuspid valve separation.

The two-dimensional echocardiographic findings in these five patients are summarized in Table I. In four patients (Cases 18–21) a dense mass was attached to the tricuspid valve (Fig. 8). In one of these patients, (Case 18) the results of a subsequent M-mode study were normal, but the two-dimensional study showed a dense mass in the area of the tricuspid valve anulus. In the fifth patient (Case 14), whose M-mode recording re-

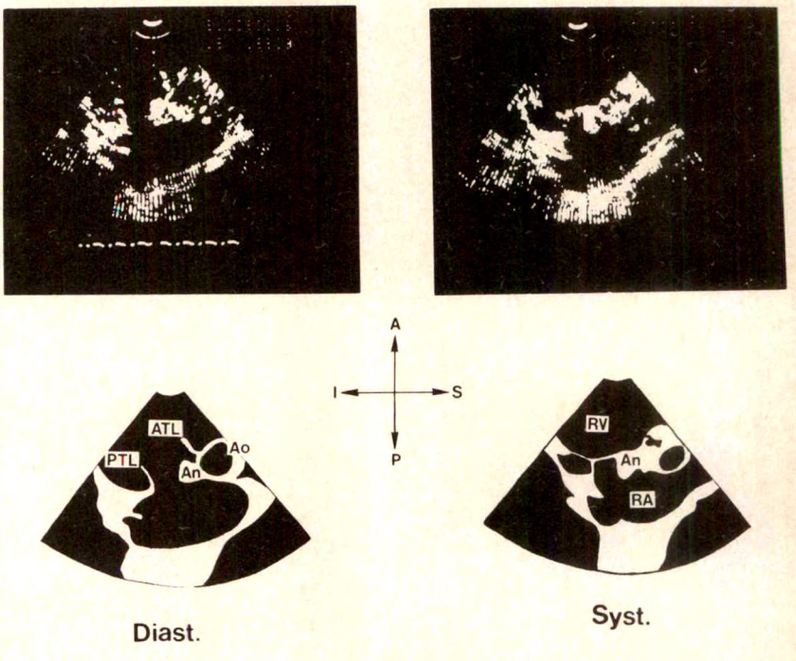


FIGURE 4. Case 5. Diastolic (Diast.) and systolic (Syst.) frames from a two-dimensional echocardiographic study of a patient with culture-negative endocarditis and a ruptured sinus of Valsalva aneurysm confirmed at surgery. Each single frame is accompanied by a labeled, idealized diagram. The aneurysm (An) appears as an outpouching from the aorta (Ao) into the right atrium (RA). The M-mode echocardiogram only showed a sclerotic aortic valve. ATL = anterior tricuspid leaflet; PTL = posterior tricuspid leaflet; RV = right ventricle; other abbreviations as in Figure 2.

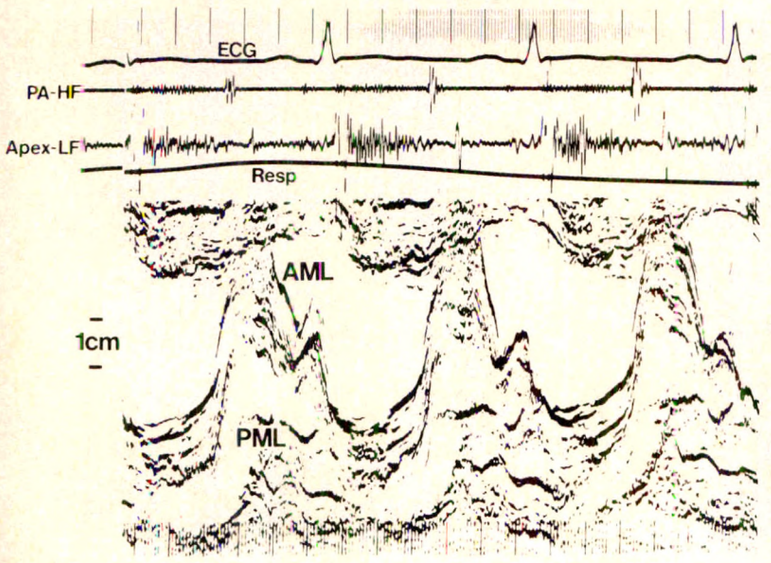


FIGURE 5. Case 15. M-mode echocardiogram from a patient with known mitral valve prolapse in whom infective endocarditis and a flail anterior mitral leaflet (AML) developed. Note the marked holosystolic prolapse and the shaggy appearance of both the anterior and posterior mitral leaflets (PML). Apex-LF = apex-low frequency phonocardiogram; ECG = electrocardiogram; PA-HF = pulmonic area-high frequency phonocardiogram; Resp = respiration.

vealed excessive systolic tricuspid valve separation, flail anterior and posterior tricuspid leaflets were seen. The sagittal view was best for detecting a vegetation or flail leaflets.

Surgical confirmation was available in two patients. Both had endocarditis; one also had flail anterior and posterior tricuspid valve leaflets.

Discussion

M-mode echocardiography: The use of M-mode echocardiography in detecting valvular vegetations was described in 1973.[4] The most characteristic M-mode appearance of a vegetation[1] is that of a nonuniform echo-producing mass attached to a valve leaflet with unrestricted and often chaotic valve motion. These echo-producing masses are usually described as "shaggy." The sensitivity of M-mode echocardiography in detecting valvular vegetations is low; the results are positive in approximately 34 percent[2] to 55 percent[3] of patients with endocarditis. In patients with infective endocarditis and clinical findings of valvular insufficiency, the M-mode echocardiographic findings are more sensitive.[5] It was suggested that the specificity of these findings is high; however, a recent report[6] indicates that features of endocarditis may be seen in most patients with the mitral valve prolapse syndrome.

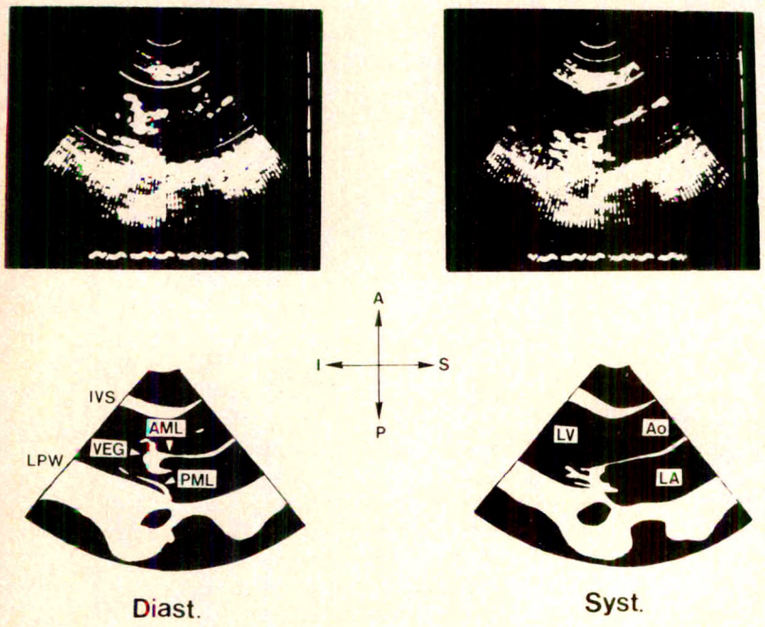


FIGURE 6. Case 15. Diastolic (Diast.) and systolic (Syst.) frames from a two-dimensional echocardiographic study of the same patient as in Figure 5. Each single frame is accompanied by a labeled, idealized diagram. The study shows a vegetation (VEG) attached to the anterior mitral leaflet and a flail anterior mitral leaflet (AML). During systole, the tip of the anterior mitral leaflet moved past the line of mitral valve closure into the left atrium (LA). These findings were confirmed at surgery. LV = left ventricle; PML = posterior mitral leaflet; other abbreviations as in Figure 2.

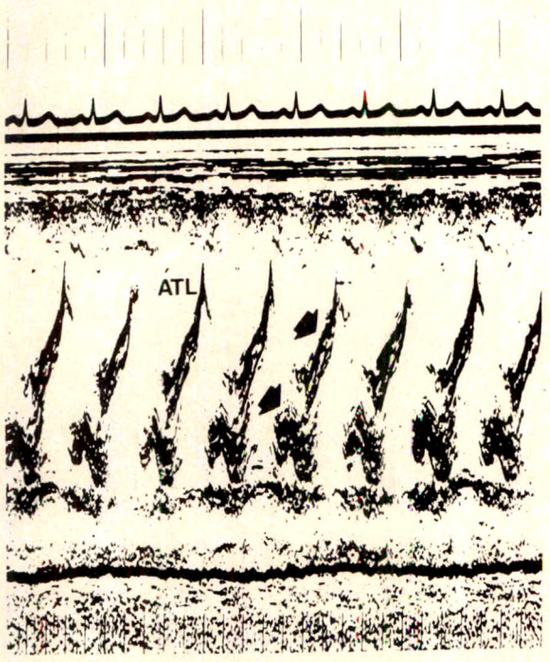


FIGURE 7. Case 19. M-mode echocardiogram from a patient with tricuspid valve endocarditis. Note the thickened anterior tricuspid leaflet (ATL). The leaflet's motion was not restricted during diastole. The vegetation is indicated by the **arrows**.

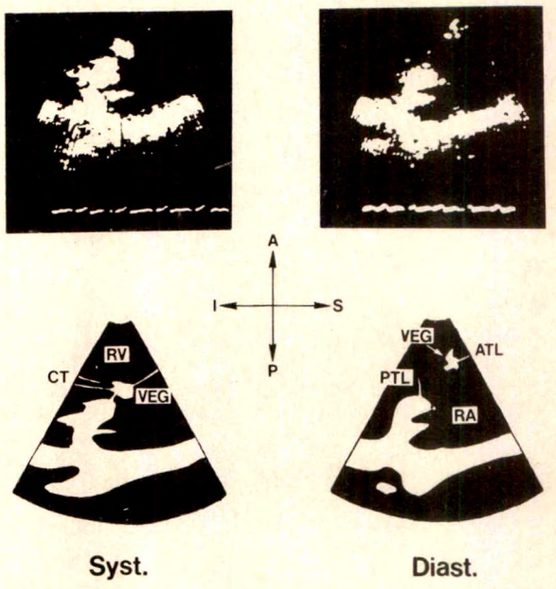


FIGURE 8. Case 19. Systolic (Syst.) and diastolic (diast.) frames from a two-dimensional echocardiographic study of the same patient as in Figure 7. Each single frame is accompanied by a labeled, idealized diagram. The study shows a vegetation (VEG) attached to the anterior tricuspid valve leaflet (ATL). When the valve opened in diastole, the vegetation moved with the leaflet into the right ventricle (RV). A vegetation was confirmed at surgery. CT = chordae tendineae; PTL = posterior tricuspid valve leaflet; RA = right atrium.

Myxomas may be confused with vegetations.[1] Valve calcification or thickening may also be confused with vegetations; conversely, valve calcification or thickening may obscure the identification of a vegetation.

M-mode echocardiography is also useful in diagnosing complications of endocarditis. An aortic root abscess may be suggested by a double density of the aortic wall.[7] The criteria for a flail aortic valve include diastolic aortic valve fluttering with prolapse of the echoes into the left ventricular outflow tract.[8] Premature closure of the mitral valve is echocardiographic evidence of the marked hemodynamic derangement of acute aortic insufficiency.[9] Systolic intracavitary left atrial echoes, fine systolic mitral valve fluttering, coarse diastolic anterior mitral valve leaflet fluttering, chaotic diastolic posterior leaflet motion and marked holosystolic mitral valve prolapse may suggest ruptured chordae tendineae.[10]

Two-dimensional vs. M-mode echocardiography: The two-dimensional features of valvular vegetations were previously described.[11] The lesions appear as rapidly oscillating masses attached to or replacing normal valve tissue. Two-dimensional studies are also useful in detecting ruptured chordae tendineae.[10]

Our 21 patients with clinical endocarditis had 22 valves involved. Vegetations were detected in 10 valves with M-mode echocardiography and in 9 valves with two-dimensional echocardiography. Thus, the sensitivity of the two techniques in detecting actual vegetations is similar (approximately 45 percent). In one patient (Case 13) the results of the M-mode study were positive for a mitral valve vegetation, but the results of the two-dimensional study were negative.

Two-dimensional echocardiography was superior to M-mode echocardiography in detecting complications of endocarditis. Complications were detected in 2 patients with M-mode echocardiography and in 10 patients with two-dimensional echocardiography ($P < 0.05$). The results of the M-mode study were positive in two of the eight patients with flail valves (five aortic, two mitral and one tricuspid). The characteristic two-dimensional finding of flail aortic valve leaflet is the displacement of all or part of the leaflet into the left ventricular outflow tract during diastole. Systolic motion was normal. In one patient (Case 5), two-dimensional echocardiography also detected another complication of aortic valve endocarditis, a sinus of Valsalva aneurysm; in this patient a pouch of the noncoronary cusp protruded into the right atrium.

Clinical implications: In this small series of patients with clinically diagnosed infective endocarditis, the sensitivity of two-dimensional echocardiography was similar to that of M-mode echocardiography in detecting valvular vegetations. The finite resolution of ultrasound may be the limiting factor in both techniques. The pathologic process may present as a destructive process rather than as a vegetative growth. Patients with false negative M-mode studies may have abnormal two-dimensional studies that detect the results of this destructive process. A two-dimensional study disclosing valvular destruction should be con-

sidered confirmational evidence in the clinical setting of infective endocarditis. Two-dimensional echocardiography was able to detect either a vegetation or evidence of valvular destruction in 16 of 21 patients (17 of 22 involved valves).

The two-dimensional echocardiographic technique is superior because of its ability to visualize areas of the cardiac valves that are "silent" to the M-mode technique and to delineate the spatial relations among cardiac structures that permit the diagnosis of valvular destruction. When the two techniques are combined, a vegetation or valvular destruction can be detected in approximately 80 percent of cases ($P < 0.05$ compared with the M-mode technique alone).

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Inotropic Effect of Post-Stimulation Potentiation in Man: An Echocardiographic Study

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To determine the magnitude of enhancement of the inotropic state in the intact human left ventricle, echocardiographic studies were performed in 11 subjects during pacing-induced changes in heart rate. Incremental atrial or ventricular pacing (80 to 160 beats/min) was performed for 1 minute at each rate, and echocardiographic variables of left ventricular function and indexes of left ventricular thickening were assessed for the post-stimulation beats and compared with the values obtained during sinus rhythm before pacing. For the first post-stimulation beat at maximal paced rates (146 ± 3 beats/min, mean ± standard error of mean), the ejection fraction (+23 percent $P < 0.001$), percent fractional shortening (+45 percent, $P < 0.001$) and mean velocity of circumferential fiber shortening (+45 percent, $P < 0.001$) increased significantly, whereas the end-systolic dimension (−22.4 percent, $P < 0.001$) and volume (−52 percent, $P < 0.001$) decreased significantly. The end-diastolic dimension (+1.42 percent) and volume (+4.8 percent) did not change significantly. Similarly, septal thickening (+21.89 percent, $P < 0.005$), posterior wall thickening (+23.4 percent, $P < 0.001$), left ventricular thickening (+21.91 percent, $P < 0.001$) and the mean rate of left ventricular thickening (+33 percent, $P < 0.001$) increased significantly. Similar significant changes, although of a lesser magnitude, occurred at lower paced rates; the magnitude of these changes was proportional to the pacing rate. Decay in potentiation occurred within four to five beats after pacing was stopped at any given rate.

Thus, in the intact human heart (1) the positive inotropic effects of stimulation on the left ventricle are reflected as post-stimulation potentiation, (2) potentiation is related to the pacing rate, and (3) decay in potentiation occurs rapidly when pacing is stopped.

The positive inotropic effects of increased contraction frequency have been well documented in isolated cardiac muscle and in the intact canine heart.[1–7] Although the direct relation between contraction frequency and contractility is well known, the level of the inotropic state can be significantly influenced by the marked decrease in ventricular end-diastolic pressure, volume and afterload induced by pacing. The purpose of this study was to elucidate, using quantitative echocardiography, the magnitude of enhancement of left ventricular contractility in the intact human heart immediately after cessation of increased contraction frequency (post-stimulation), when end-diastolic dimensions and volume returned toward control values. The use of quantitative echocardiography enabled us to assess (1) left ventricular cavity size and volume changes, (2) variables of left ventricular function, and (3) indexes of left ventricular wall thickening—a specific measure of contractility.

Methods

Patients: Eleven patients aged 36 to 62 years were studied. The experimental nature of the procedure was explained to all patients and signed consent was

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TABLE I

Changes in Dimensions, Volumes and Indexes of Left Ventricular Function

	Rate (beats/min)	Mean BP (mm Hg)	PSi (msec)	Dd (cm)	Ds (cm)	EDV (cc/beat)	ESV (cc/beat)	% Δ D	EF (%)	Mean Vcf (circ/sec)
Control values	70 ± 3.2	97 ± 5.5	...	4.9 ± 0.17	3.3 ± 0.13	123 ± 0.10	38 ± 4	33 ± 1.4	69 ± 2	1.1 ± 0.05
After pacing	90 ± 2.3	95 ± 6.7	1297 ± 66	5.06 ± 0.22	3.0 ± 0.14	137 ± 17	31 ± 4	39 ± 1.2	77 ± 1.5	1.35 ± 0.05
% change	...	...	...	+3.2	−9	+11.3	−18.42	+18	+11.59	+22.72
P value	...	NS	...	NS	0.005	NS	<0.01	<0.005	<0.001	<0.001
After pacing	121 ± 2	82 ± 5.7	1170 ± 86	4.84 ± 0.17	2.64 ± 0.15	118 ± 11	20.3 ± 3	44 ± 1.7	81 ± 1.7	1.52 ± 0.04
% change	...	...	...	−1.22	−20	−4	−47.36	+33.33	+17.39	+38.18
P value	...	<0.01	...	NS	<0.001	NS	<0.001	<0.001	<0.001	<0.001
After pacing	146 ± 3	80 ± 3.3	1168 ± 66	4.97 ± 0.2	2.56 ± 0.14	129 ± 13	18.4 ±3.2	48 ± 2	85 ± 1.7	1.69 ± 0.08
% change	...	...	...	+1.42	−22.42	+4.8	−52	+45	+23	+54
P value	...	<0.025	...	NS	<0.001	NS	<0.001	<0.001	<0.001	<0.001

Data are expressed as mean values ± standard error of the mean.
BP = blood pressure; Circ/sec = circumferences/second; Dd = end-diastolic dimension; Ds = end-systolic dimension; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; NS = not significant; % Δ D = percent fractional shortening; *P* = probability; PSi = post-stimulation interval; Vcf = circumferential fiber shortening rate.

obtained. Seven of the 11 patients underwent diagnostic electrophysiologic studies, and the other 4 patients underwent left heart catheterization for atypical chest pain. The criteria for selection in the study included (1) normal resting electrocardiograms, chest X-ray film, treadmill test (11 patients) and coronary arteriograms (4 patients); (2) normal echocardiographic ejection fraction (greater than 60 percent); and (3) technically superior echocardiograms with optimal visualization of both sides of the interventricular septum and the endocardial and epicardial surfaces of the left ventricular posterior wall.

Experimental protocol: A no. 6 quadripolar catheter was introduced percutaneously into an antecubital vein and positioned in the right ventricular apex or outflow tract (seven patients) or in the high right atrial region (four patients) under fluoroscopic guidance and electrocardiographic monitoring. Incremental atrial or ventricular pacing was begun at a rate 10 beats/min greater than the spontaneous sinus rate and increased by 10 beats/min up to a maximal rate of 150 to 160 beats/min. Each paced atrial or ventricular rate was maintained for approximately 1 minute, and then sinus rhythm was allowed to return after sudden cessation of pacing. Sinus rhythm was maintained for another minute before the next pacing rate was begun. Blood pressure was determined with the cuff technique at all phases of pacing.

Echocardiograms were continuously recorded using a Smith-Kline 20 ultrasonoscope and a 2.25 megahertz piezoelectric transducer, 0.5 inch in diameter and focused at 7.5 cm. The repetition rate of the transducer was 1,000 impulses/sec. The patients were studied in the supine position with the transducer in the fourth or fifth intercostal space just to the left of the sternum. The transducer was directed posteriorly and medially until the pattern of mitral valve motion was seen. The transducer was then directed laterally and inferiorly to obtain echoes of the endocardial surfaces of the septum and the left ventricular posterior wall. The echocardiograms and a simultaneous electrocardiographic lead II, a phonocardiogram and a carotid pulse tracing were recorded continuously on a Honeywell 1856 Visicorder at a paper speed of 50 mm/sec and on an Electronics for Medicine Dr 12 multichannel oscilloscope at paper speeds of 50, 75 and 100 mm/sec. The phonocardiograms and the carotid pulse tracings were recorded using Electronics for Medicine pulse transducers. The time constant of the transducer for the carotid pulse tracing was greater than 2.2 seconds. In four patients a simultaneous left ventricular pressure tracing was also recorded.

Measurements and calculations: All echocardiographic measurements were made at the level of the posterior mitral valve supporting apparatus. The left ventricular dimensions were measured from the endocardial echo of the posterior wall to the endocardial echo of the left side of the interventricular septum. The end-diastolic dimension (Dd) was measured at the peak of the QRS complex. The end-systolic dimension (Ds) was taken as the smallest distance separating left ventricular endocardial surfaces. Left ventricular volumes at end-diastole (EDV) and end-systole (ESV) were calculated as the cube of the respective dimensions.

Percent fractional shortening (%Δ D) was calculated as: %Δ D = (Dd-Ds)/Dd × 100.

Ejection fraction (*EF* %) was calculated as: EF % = (EDV − ESV)/EDV. The mean circumferential fiber shortening rate (mean Vcf) was calculated as: mean Vcf (circumferences/sec) = (Dd-Ds)/LVET × Dd, where LVET = left ventricular ejection time.

Indexes of thickening: *Septal thickening* (*ST*) was expressed as the ratio of the maximal total septal thickness during systole (SThs) to the end-diastolic septal thickness (SThd).[8]

TABLE II

Changes in Indexes of Thickening

	Rate (beats/min)	ST	PWT	ST/PWT	LVT	VLVT (sec^{-1})
Control values	70 ± 3.2	1.37 ± 0.05	1.58 ± 0.05	0.872 ± 0.05	1.46 ± 0.03	1.01 ± 0.04
After pacing	90 ± 2.3	1.52 ± 0.06	1.72 ± 0.06	0.896 ± 0.06	1.61 ± 0.03	1.12 ± 0.06
% change	...	+10.94	+8.86	+2.75	+10.27	+10.89
P value	...	<0.005	<0.005	NS	<0.001	<0.01
After pacing	121 ± 2	1.63 ± 0.07	1.84 ± 0.11	0.915 ± 0.07	1.75 ± 0.06	1.3 ± 0.05
% change	...	+18.97	+16.45	+4.93	+19.86	+28.71
P value	...	<0.001	<0.025	NS	<0.001	<0.005
After pacing	146 ± 3	1.67 ± 0.09	1.95 ± 0.10	0.880 ± 0.08	1.78 ± 0.05	1.35 ± 0.06
% change	...	+21.89	+23.4	+0.9	+21.91	+33
P value	...	<0.005	<0.001	NS	<0.001	<0.001

Data are expressed as mean values ± standard error of the mean. LVT = left ventricular thickening; NS = not significant; *P* = probability; PWT = posterior wall thickening; ST = septal thickening; VLVT = mean normalized rate of left ventricular thickening.

Posterior wall thickening (*PWT*) was expressed as the ratio of the maximal total posterior wall thickness in systole (PWThs) to the posterior wall end-diastolic thickness (PWThd). To determine the contribution of the septum and the left ventricular posterior wall to the left ventricular thickening (LVT), the ratio ST/PWT was calculated. Thus, if both structures contribute equally, the value of ST/PWT is 1, if the contribution of the septum is greater than that of the posterior left ventricular wall, the value is greater than 1, and if the contribution of the posterior left ventricular wall is greater, the value is less than 1.

Left ventricular thickening (*LVT*) was calculated as: LVT = (SThs + PWThs)/(SThd + PWThd).

The mean normalized rate of left ventricular thickening (*VLVT*) was calculated as: VLVT (sec^{-1}) = LVT/Dd × LVET.

Measurements and calculations were made (1) for five sinus beats before pacing and for four to five beats after cessation of pacing, and (2) only when adequate echocardiograms were available for detailed analysis. Because good echocardiograms could not be obtained at the same rates in all patients, the results indicate the values for the post-stimulation beat at minimal, intermediate and maximal pacing rates. Data were analyzed by using Student's *t* test for paired data. The results are expressed as mean values ± standard error of mean.

Results

Cumulative data during sinus rhythm before pacing and for the first post-stimulation beat at minimal (90 ± 2.3 beats/min), intermediate (121 ± 2 beats/min) and maximal (146 ± 3 beats/min) rates are presented in Tables I and II. The data in this study are expressed as mean values ± standard error of the mean.

Post-stimulation interval of the post-stimulation beat (Table I): The post-stimulation interval of the first post-stimulation beat was 1,297 ± 66 msec (range 918 to 1,580) for minimal paced rates of 90 ± 2.3 beats/min. The post-stimulation interval decreased slightly but insignificantly for intermediate and maximal pacing rates.

Changes in left ventricular cavity size and volume (Table I, Fig. 1 and 2): The control end-diastolic dimension was 4.9 ± 0.17 cm (range 3.29 to 5.33), and the end-diastolic volume was 123 ± 10 cc (range 36 to 151). During pacing, end-diastolic dimension and volume decreased. For the post-stimulation beat at all pacing rates, end-diastolic dimension and volume did not change significantly, although end-diastolic dimension varied at different rates. In contrast, end-systolic dimension and volume decreased markedly and significantly for the first post-stimulation beat at all pacing rates. The greatest decrease in end-systolic dimension and volume for the post-stimulation beat occurred at maximal paced rates.

Changes in derived indexes of left ventricular function (Table I): A significant increase in percent fractional shortening (+18 percent, $P < 0.005$), ejection fraction (+11.59 percent, $P < 0.001$) and mean velocity of circumferential fiber shortening (+22.72 percent, $P < 0.001$) occurred for the first post-stimulation beat at minimal paced rates. Furthermore, all ejection phase indexes increased progressively for the post-stimulation beat at increasing rates, and the greatest change occurred at maximal paced rates.

Changes in thickening indexes (Table II): *During control,* septal thickening was 1.37 ± 0.05 (range 1.2 to 1.75) and posterior wall thickening was 1.58 ± 0.05 (range 1.31 to 1.91). The ratio of septal thickening to posterior wall thickening was 0.872 ± 0.05. *For the post-stimulation beat,* septal and posterior wall thickening increased significantly at all paced rates. The increase in septal and posterior wall thickening was progressive and was greatest at maximal paced rates. The ratio of septal thickening to posterior wall thickening showed a −0.9 to +4 percent change; however, these changes were not statistically significant. During control studies, left ventricular thickening was 1.46 ± 0.03 (range 1.27 to 1.64), and the mean normalized rate of left ventricular thickening was 1.01 ± 0.04 sec^{-1} (range 0.78 to 1.28 sec^{-1}).

For the post-stimulation beat, left ventricular thickening and the mean normalized rate of left ventricular thickening increased progressively at increasing rates. The largest increase for the post-stimulation beat occurred at maximal paced heart rates. There was an expected significant correlation between left ventricular thickening and percent fractional shortening ($r = 0.720$,

$P < 0.001$, no. = 44) and between the mean velocity of circumferential fiber shortening and the mean normalized rate of left ventricular thickening ($r = 0.622$, $P < 0.001$, no. = 44) during control and for the post-stimulation beat at all pacing rates.

Decay in left ventricular potentiation: Figure 3 is a representative echocardiogram and left ventricular pressure tracing demonstrating the change in left ventricular dimensions, left ventricular pressure and septal and posterior wall thickening for a sinus beat before pacing and for four sinus beats after the interruption of atrial pacing at a rate of 110 beats/min. The end-diastolic pressure decreased markedly during pacing but attained control values for the first post-stimulation

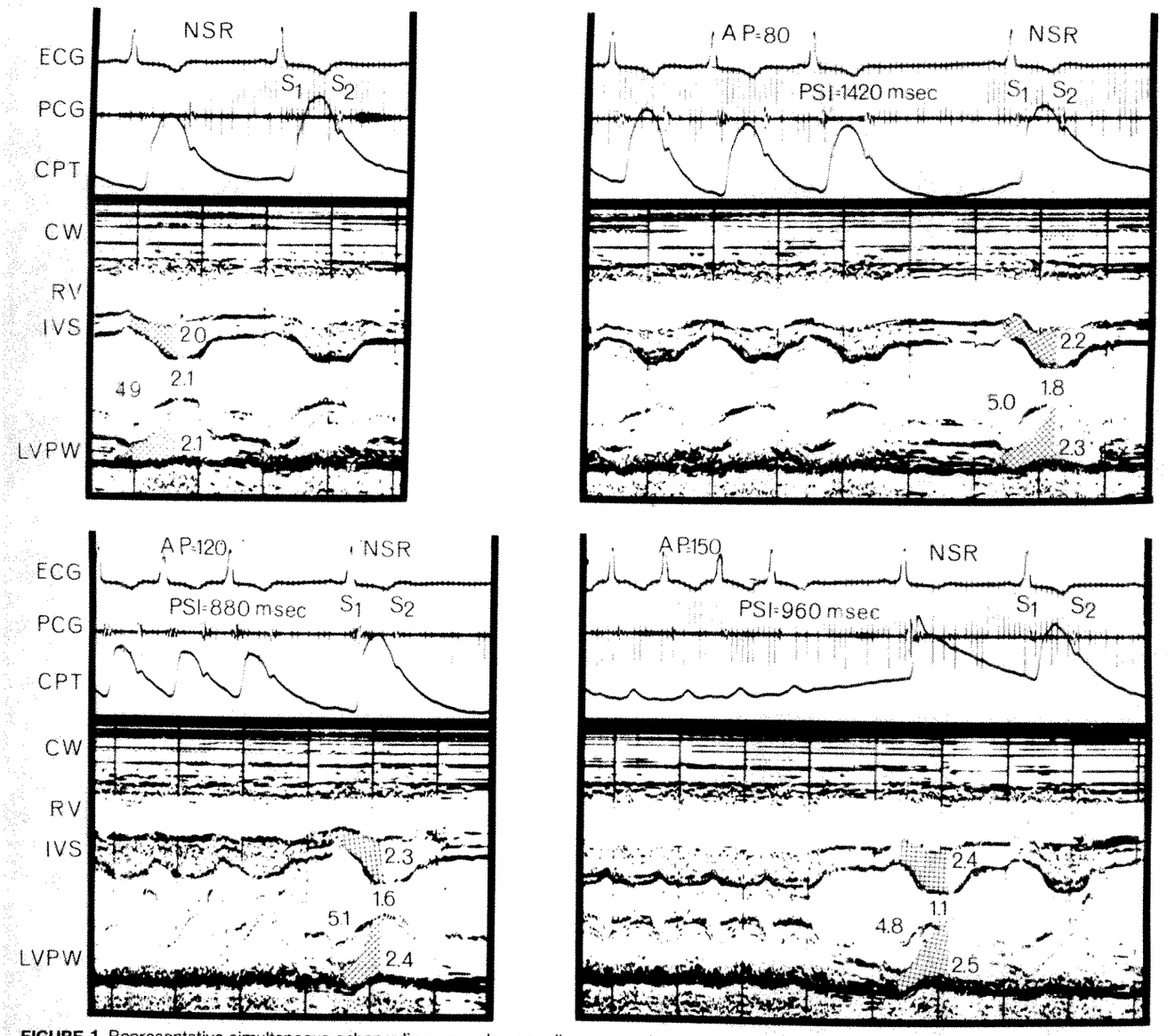


FIGURE 1. Representative simultaneous echocardiograms, phonocardiograms and carotid pulse tracings demonstrating dimensional and thickening changes during control sinus rhythm (NSR) and for the post-stimulation beat after cessation of atrial pacing (at rates of 80 to 150 beats/min). From **top to bottom in all panels,** ECG = electrocardiographic lead II; PCG = phonocardiogram; CPT = carotid pulse tracing; CW = chest wall; RV = right ventricular cavity; IVS = interventricular septum; and LVPW = left ventricular posterior wall. The **cross-hatched areas** represent the change in septal and posterior wall thickness from end-diastole to maximal thickness in systole. During control sinus rhythm (**top left panel**), the end-diastolic and end-systolic dimensions were 4.9 and 2.1 cm, respectively. Septal thickening and posterior wall thickening were 2.0 and 2.1, respectively. After cessation of atrial pacing (AP) at a rate of 80 beats/min (**top right panel**), the post-stimulation beat demonstrated a decrease in end-systolic dimension and an increase in both septal (2.2) and posterior wall thickening (2.3) compared with the control sinus beat. After cessation of atrial pacing at a rate of 120 beats/min (**bottom left panel**), the post-stimulation beat demonstrated a slight increase in end-diastolic dimension but a further marked decrease in end-systolic dimension (1.6 cm) and increases in both septal (2.3) and posterior wall thickening (2.4) compared with the control sinus beat. The post-stimulation beat after atrial pacing at a rate of 150 beats/min demonstrated a further decrease in end-systolic dimension (1.1 cm) and a further increase in both septal and posterior wall thickening. Note the progressive decrease in left ventricular cavity size during incremental atrial pacing and the poor septal motion and thickening during atrial pacing at a maximal rate of 150 beats/min. Although the end-diastolic dimension did not change appreciably for the post-stimulation beat at all rates, the changes in end-systolic dimension and septal and posterior wall thickening increased at progressively increasing rates. PSI = post-stimulation interval.

beat. A progressive decay in potentiation started at the second post-stimulation beat and reached control values by the fourth post-stimulation beat, as indicated by the changes in septal thickening, posterior wall thickening, end-systolic dimension and derived indexes of left ventricular function. Decay in potentiation occurred within four to five beats after pacing at any given rate in all patients.

Discussion

Echocardiography is a valuable noninvasive tool for the assessment of qualitative and quantitative dynamic events of the left ventricular chamber walls.[9] Echocardiographically-determined left ventricular volumes and ejection phase indexes of contractility correlate well with their cineangiographic counterparts in the absence of wall motion abnormalities.[10–14] The value of echocardiographically determined indexes of left ventricular function in assessing acute changes in inotropy and alterations in preload and afterload were also amply documented.[15–18] The echocardiographic observation of septal and posterior wall thickening has generated considerable interest recently.[19] To assess the effects of post-stimulation potentiation in man in this study, we used conventional variables of echo wall motion and also derived indexes of septal, posterior wall and left ventricular thickening. Thickening may be a more accurate indicator of contractility than wall motion, which is affected by a host of factors[20–25]; therefore we applied the concept of "normalized velocity" to thickening to obtain a mean rate of left ventricular thickening.

The effect of stimulation on the post-stimulation beat: Increases in heart rate produced by incremental atrial or ventricular pacing, or both, result in progressive decreases in left ventricular end-diastolic pressure, dimension and volume.[8,26–31] The changes in end-diastolic fiber length as a result of pacing can significantly influence the level of inotropic state. In anesthetized as well as conscious animals, when changes in fiber length were prevented by a rapid volume infusion, enhanced

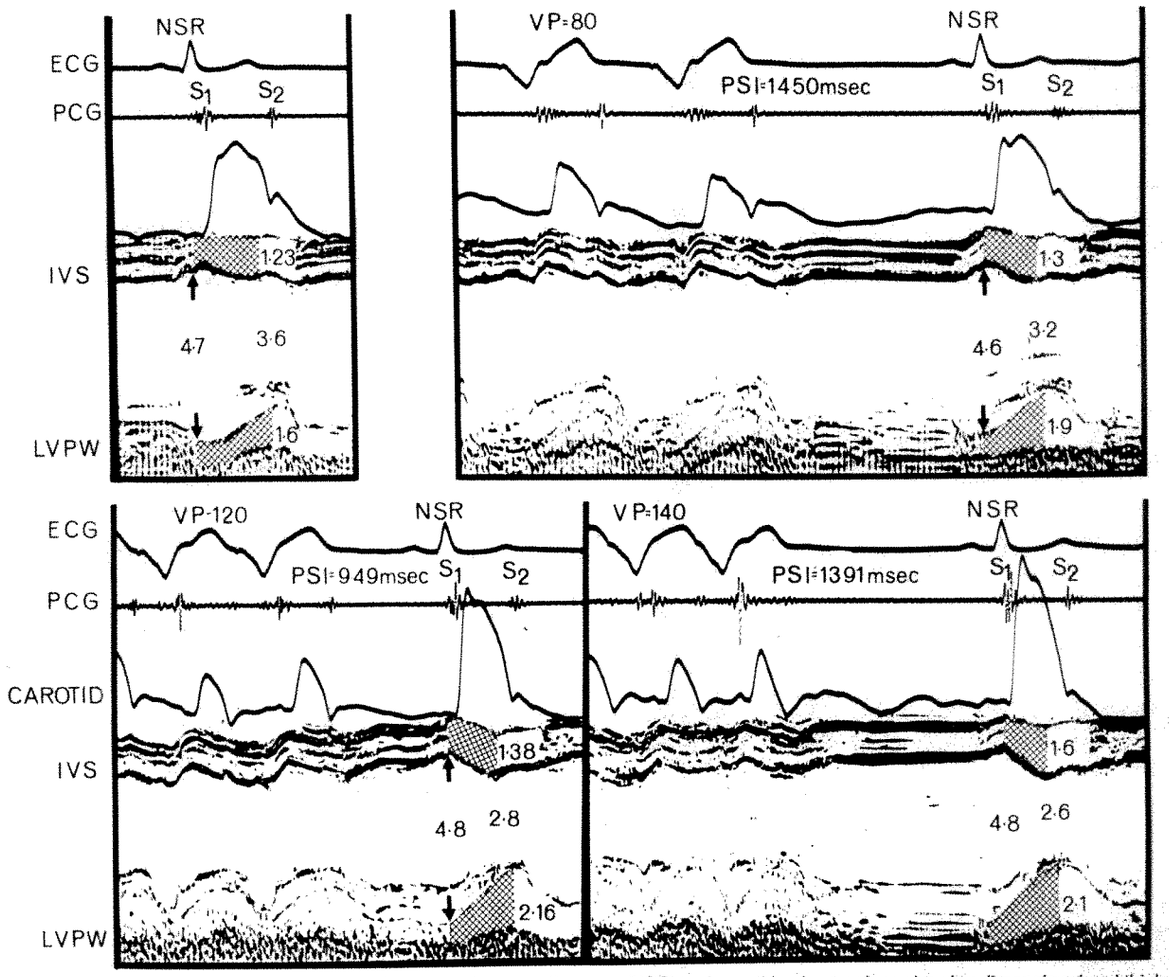


FIGURE 2. Representative simultaneous echocardiograms, phonocardiograms (PCG) and carotid pulse tracings showing dimensional and thickening changes during control sinus rhythm and for the post-stimulation beat after cessation of ventricular pacing (VP) at rates of 80 to 140 beats/min. There was a marked and progressive decrease in the end-systolic dimension for the post-stimulation beat at increasing rates, whereas the end-diastolic dimension did not change appreciably compared with control sinus rhythm. Increases in septal and posterior wall thickening for the post-stimulation beat are evident. Note the abnormal motion of the interventricular septum (IVS) and a progressive decrease in left ventricular internal dimensions during apical ventricular pacing. Abbreviations as in Figure 1.

ventricular performance occurred, as suggested by the increased development of force and velocity.[6,32] However, rapid volume infusions can induce reflex changes that may in themselves induce changes in contractility.[33] Sonnenblick et al.[34] determined the effects of heart rate on the dynamics of force development in the human right ventricle during corrective intracardiac surgery. As the heart rate was increased from 72 to 145 beats/min, peak contractile force did not change significantly; however, the maximal rate of force development (dP/dt) increased progressively. Therefore, they postulated that in humans changes in heart rate produce a "velocity staircase" rather than a "force staircase."

We previously demonstrated that ventricular pacing results in an abnormal septal contraction pattern (caused by the altered activation sequence) and a progressive decrease in ejection septal thickening. We also observed decreased septal motion and thickening during incremental atrial pacing, particularly at high rates. These changes in contraction pattern induced by pacing limit the assessment of left ventricular function with echocardiography during pacing studies. Because end-diastolic dimensions and volumes returned toward control values after cessation of pacing and for the reasons discussed earlier, we assessed echocardiographic variables of left ventricular function for the post-stimulation beat as a measure of inotropic potentiation. Our findings indicate that (1) stimulation of either the right ventricle or the right atrium augments left ventricular contractility, as indicated by significant increases in ejection phase indexes of contractility and left ventricular wall thickening of the post-stimulation beat, (2) potentiation is evident at rates slightly greater than the basal sinus rate and is proportional to the rate of pacing, and (3) decay in potentiation occurs within four to five beats after cessation of pacing.

These observations in man are in keeping with the findings in isolated muscle preparation that the magnitude of increase in force or velocity after lowering heart rate referred to as "post-stimulation" is directly proportional to the preceding rate of contraction. Mahler et al.[7] demonstrated 16 and 22 percent increases in left ventricular dP/dt and mean velocity of circumferential fiber shortening, respectively, in the conscious dog in association with a decrease in left ventricular end-diastolic pressure during an average increase in heart rate from 90 to 158 beats/min (+71 percent). However, for the first post-pacing beat when left ventricular end-diastolic pressure had returned to near control values, left ventricular dP/dt increased 35 percent and mean velocity of circumferential fiber shortening increased 32 percent above control values. It is interesting that our findings in man are similar to those reported by Mahler et al.[7] in the dog. Thus, for an av-

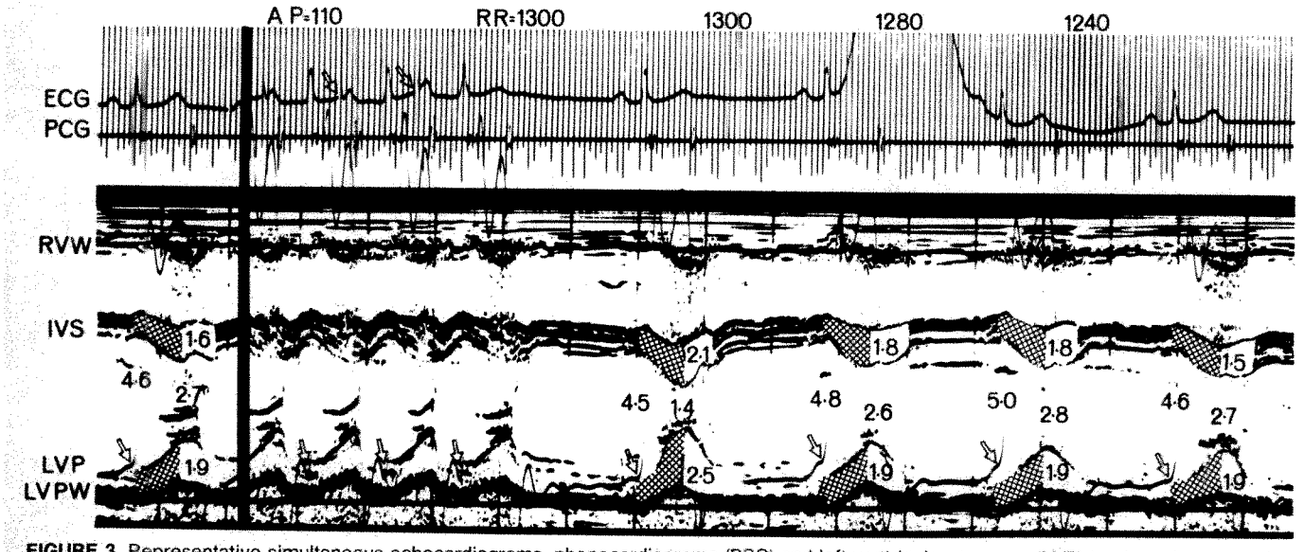


FIGURE 3. Representative simultaneous echocardiograms, phonocardiograms (PCG) and left ventricular pressure (LVP) tracings demonstrating decay in left ventricular potentiation after atrial pacing (AP) at a rate of 110 beats/min. During control sinus rhythm, the end-diastolic and end-systolic dimensions were 4.6 and 2.7, respectively, and septal and posterior wall thickening were 1.6 and 1.9, respectively. The calculated ejection fraction, percent fractional shortening and mean circumferential fiber shortening rate (Vcf) were 80 percent, 41 percent and 1.19 circumferences/sec, respectively. During atrial pacing (rate 110 beats/min), note the marked decrease in end-diastolic pressure (**open arrows**) compared with control. After atrial pacing for the first post-stimulation beat, the end-diastolic pressure and dimension returned to near control value, whereas the end-systolic dimension decreased markedly (1.4 cm), resulting in a marked increase in the ejection fraction (97 percent), percent fractional shortening (69 percent) and mean Vcf (1.82 circumferences/sec). For the second post-stimulation beat, end-diastolic pressure and end-diastolic and end-systolic dimensions increased; septal and posterior wall thickening decreased; and the ejection fraction, percent fractional shortening and mean Vcf were 84 percent, 46 percent and 1.29 circumferences/sec, respectively. For the third post-stimulation beat, the ejection fraction (82 percent), percent fractional shortening (44 percent) and mean circumferential fiber shortening rate (1.22 circumferences/sec) decreased further. For the fourth post-stimulation beat, the end-diastolic and end-systolic dimensions and septal and posterior wall thickening attained control value. The ejection fraction (80 percent), percent fractional shortening (41 percent) and mean circumferential fiber shortening rate (1.15 circumferences/sec) also attained control values. Abbreviations as in Figure 1.

erage increase in heart rate of 73 percent (from 70 ± 3 to 121 ± 3 beats/min), percent fractional shortening, ejection fraction and mean velocity of circumferential fiber shortening increased 33.33, 17.37 and 38 percent, respectively. With an even larger increase in heart rate of 108 percent (from 70 ± 3.2 to 146 ± 3 beats/min), percent fractional shortening, ejection fraction and mean velocity of circumferential fiber shortening rate increased 45, 23 and 54 percent, respectively.

Mechanism of enhanced potentiation of post-stimulation beat: The force-velocity relation during left ventricular ejection is influenced by (1) the inotropic state of the left ventricle, and (2) alterations in preload and afterload. Our observations suggest that the enhanced potentiation of the post-stimulation beat is due to an enhanced inotropic state of the left ventricle and is partly related to decreases in left ventricular afterload. It is unlikely that changes in preload had any effect on potentiation because end-diastolic dimension and volume did not change significantly for the post-stimulation beat at all pacing rates. The latter finding is probably related to the fact that end-diastolic dimension and volume are markedly reduced during pacing and return to near control values for the first post-pacing beat despite a long diastolic pause. The marked and significant increase in percent fractional shortening and ejection fraction was primarily related to marked end-systolic shortening. Also, the significant increase in septal and posterior wall thickening strongly suggest an enhanced inotropic state. The rapid decay in potentiation in association with increasing R-R intervals or left ventricular end-diastolic dimension, or both, suggest that alteration of preload did not influence changes in ejection phase indexes of contractility for the post-stimulation beat. It is also possible that enhanced potentiation could be related to the release of catecholamines during pacing, particularly at rapid rates. However, because of the rapid decay in potentiation and the observation that potentiation could be elicited at rates slightly greater than that of sinus rhythm, the latter mechanism is unlikely. Also, Mahler et al.[7] demonstrated expected responses to increased heart rate in the conscious dog even after blocking doses of propranolol.

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Role of Blood Viscosity in the Production of Innocent Ejection Murmurs

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The purpose of this study was to investigate factors that may participate in the production of innocent ejection murmurs. Although it is known that ejection murmurs are produced by turbulent flow, the cause of turbulence in subjects with innocent murmurs has not been determined. The viscosity and the density of blood are factors that participate in the production of turbulence. Therefore, their role in the production of innocent ejection murmurs was investigated in 40 healthy young women, aged 18 to 22 years. Fourteen subjects had an innocent murmur; 26 had no murmur. All had a normal hematocrit (37 ml/100 ml or greater); none were anemic. However, the subjects with an innocent murmur had a significantly lower hematocrit ($P < 0.01$), and consequently the viscosity of blood in these subjects was lower (0.038 ± 0.001 versus 0.042 ± 0.001 poise) ($P < 0.001$). The density of blood and the estimated stroke volume were similar in both groups. These observations suggest that young women with an innocent murmur may have a lower viscosity of blood than those without a murmur. The increased turbulence caused by the decreased viscosity may contribute to causing inaudible ejection murmurs to exceed the threshold of audibility.

Although innocent ejection murmurs are a common auscultatory finding, particularly in children and adolescents,[1,2] the mechanism of such murmurs has not been determined. By definition, innocent ejection murmurs are murmurs heard at rest in subjects with no apparent cardiac abnormality.[3] Innocent ejection murmurs are short systolic murmurs, usually heard with maximal intensity in the second left intercostal space.[4] Murmurs due to recognized physiologic circumstances that produce high flow are usually considered flow murmurs and are excluded from this definition of innocent murmurs. Consequently, ejection murmurs in anemic patients or patients with a high output state such as thyrotoxicosis are defined as flow murmurs. Such murmurs are differentiated from innocent ejection murmurs on the basis of the accompanying clinical condition. It is clear that ejection murmurs are produced by turbulent flow.[5] The viscosity and density of blood are rheologic factors known to participate in the production of turbulence and believed to contribute to murmurs.[6,7] Therefore, we investigated the effects of blood viscosity and density on the production of innocent ejection murmurs.

Methods

Subjects: Observations on the role of blood viscosity in the genesis of innocent ejection murmurs were made in 40 healthy volunteer female student nurses and laboratory technicians aged 18 to 22 years. Fourteen subjects were found to have an innocent ejection murmur; 26 had no murmur. All of the subjects were examined by two physicians, who agreed on the presence, location and characteristics of the murmurs. Each subject was carefully examined in a quiet room in the sitting, supine and right anterior oblique positions. Subjects were considered to have an innocent ejection murmur if a short early or mid systolic

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TABLE I

Characteristics of Subjects Studied

	Control Subjects (no. = 26)	Subjects With Innocent Murmurs (no. = 14)
Age (yr)		
Mean	20	20
SEM	0.2	0.3
Range	18–22	18–22
P		NS
Height (inches)		
Mean	65	64
SEM	0.4	0.5
Range	61–69	60–68
P		NS
Weight (lb)		
Mean	126	123
SEM	4	3
Range	95–200	110–142
P		NS
Heart rate (beats/min)		
Mean	77	77
SEM	2	2
Range	60–102	64–100
P		NS
Blood pressure (mm Hg)		
Mean	110/71	113/71
SEM	2/2	3/2
Range	96–130/60–88	100–138/60–84
P		NS/NS
Transverse Diameter (cm)		
Mean	10.8	10.0
SEM	0.2	0.7
Range	9.0–12.7	9.0–12.4
P		NS
Cardiothoracic ratio (%)		
Mean	0.40	0.40
SEM	0.01	0.01
Range	0.36–0.48	0.33–0.47
P		NS
Stroke volume (ml/stroke)		
Mean	60	53
SEM	4	4
Range	22–91	29–78
P		NS

NS = not significant; *P* = probability; SEM = standard error of the mean.

murmur was heard at the base of the heart with the subject at rest. All of the subjects in this study had murmurs of grade I intensity (of grades I through VI). Subjects were excluded if a murmur was heard with maximal intensity at the apex or if a murmur radiated to the carotid vessels. Subjects with supraclavicular arterial bruits, mammary souffles, venous hums, musical murmurs and late systolic murmurs were also excluded.[4] All subjects had normal splitting of the second heart sound and several had a physiologic third sound. Subjects were excluded if a systolic click or diastolic murmur was heard. No subject had a left or right ventricular impulse or pectus excavatum.

All subjects were active and normotensive, with no history of cardiac or pulmonary disease, and all had a normal electrocardiogram, chest roentgenogram and echocardiogram. No subject was taking any medication other than contraceptive agents. Subjects were excluded if they had a history of rheumatic fever or scarlet fever or a family history of congenital heart disease. Echocardiography or physical examination

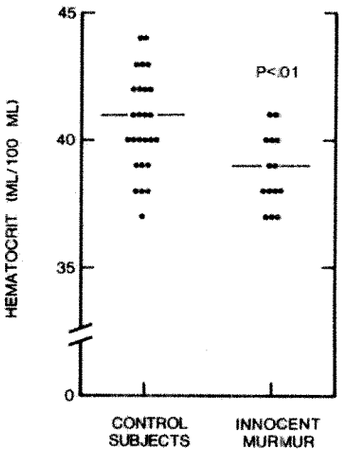


FIGURE 1. Hematocrit of control subjects and subjects with an innocent ejection murmur.

revealed a prolapse of the mitral valve in some subjects, who were also excluded. Subjects with a hematocrit lower than 37 ml/100 ml, which is considered the lower limit of normal for women,[8] were also excluded.

Echocardiography: In each subject an echocardiogram was obtained with an Electronics for Medicine V3270 echocardiograph, using a 3.5 megahertz transducer. Tracings were recorded on an Electronics for Medicine VR 12 recorder at a paper speed of 50 mm/sec with the subject in the left lateral position, between 20 and 45 degrees. The transducer was placed at the third to fifth left intercostal space, and sweeps were made from the aortic root to the mitral valve and toward the apex of the left ventricle. The left ventricular internal dimension was measured at the level of the chordae of the mitral valve during diastole at the peak of the R wave of the electrocardiogram and during peak systole using standard methods.[9] The stroke volume was calculated from echocardiograms using equations based on the assumption that the ventricle has the configuration of a prolate ellipse.[9]

Blood studies: The hematocrit was measured with the microhematocrit method from a sample of venous blood. The viscosity of both whole blood and plasma were measured at 37°C at a shear rate of 180 sec^{-1} with a Brookfield cone-in-plate rheolog viscometer (Stoughton, Massachusetts). The density of blood (g/cm^3) was measured by weighing 10 ml of blood on a Mettlar balance (Princeton, New Jersey).

Results

The age, heart rate, blood pressure, height and weight were similar in the subjects with and without an innocent ejection murmur (Table I). The transverse diameter and the cardiothoracic ratio determined with plain chest roentgenography and the stroke volume estimated from the echocardiogram did not differ significantly in the two groups (Table I).

Although all subjects had a normal hematocrit, those with an innocent ejection murmur had a lower hematocrit than those without a murmur (39 ± 0.5 versus 41 ± 0.4 ml/100 ml) (mean ± standard error of the mean) ($P < 0.01$, unpaired t test) (Fig. 1).

The viscosity of whole blood was lower in subjects with an innocent ejection murmur (0.038 ± 0.001 versus

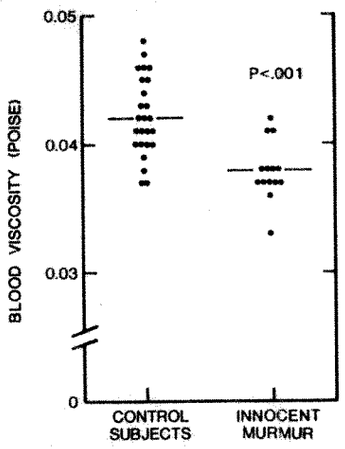


FIGURE 2. Viscosity of blood of control subjects and subjects with an innocent ejection murmur.

0.042 ± 0.001 poise) (mean ± standard error of the mean) (P <0.001) (Fig. 2). The plasma viscosity was also lower in subjects with an innocent murmur (0.013 ± 0.0001 versus 0.014 ± 0.0002 poise) (P <0.001). The density of blood was the same in both groups (1.02 ± 0.01 g/ml) (Table II).

TABLE II

Hematocrit, Viscosity and Density of Blood in Subjects Studied

	Control Subjects	Subjects With Innocent Murmurs
Hematocrit (ml/100 ml)		
Mean	41	39
SEM	0.4	0.5
Range	37–44	37–42
P		<0.01
Blood viscosity (poise)		
Mean	0.042	0.038
SEM	0.001	0.001
Range	0.037–0.048	0.033–0.042
P		<0.001
Plasma viscosity (poise)		
Mean	0.014	0.013
SEM	0.0002	0.0001
Range	0.013–0.017	0.013–0.014
P		<0.001
Blood density (poise)		
Mean	1.02	1.02
SEM	0.01	0.01
Range	0.97–1.04	0.99–1.06
P		NS

NS = not significant; P = probability; SEM = standard error of the mean.

Discussion

Factors affecting blood turbulence: Because ejection murmurs are produced by turbulent blood flow,[5] an exploration of factors related to the development of turbulence may contribute to an understanding of the cause of such murmurs. In steady pipe flow, the factors known to affect turbulence are density, velocity, diameter and viscosity. Whole blood viscosity clearly differed in the subjects with an innocent ejection murmur and the control subjects without a murmur. The diminished blood viscosity observed in subjects with an innocent ejection murmur increases the tendency toward turbulent flow and thus may contribute to the production of a murmur.

Additional factors probably contribute to turbulence in the region of the semilunar valves. The normal valve leaflets project into the stream of flow and initiate turbulence.[10] The pulsatile nature of flow, branching, curvature and tapering of vessels, as well as compliant walls, also affect the characteristics of flow, although the magnitude of these effects has not been clearly determined.[11] Abnormally stiff or inflexible erythrocytes may also contribute to turbulence.[12] Even the number of erythrocytes has an effect on turbulence beyond the effect of erythrocytes on viscosity.[13] Irrespective of the effects of any of these factors (pulsatile flow, vessel geometry, and the number of characteristics of erythrocytes), a decrease in blood viscosity tends to augment turbulence.

Blood viscosity and threshold of audibility of turbulent flow: It was demonstrated that innocent ejection murmurs can be identified in almost all normal subjects with the use of an amplifying microphone.[2] It appears that the increased turbulence resulting from the lower viscosity of blood in patients with innocent murmurs is sufficient to cause the sound to exceed the threshold of audibility. High frequency pressure fluctuations are an intrinsic characteristic of turbulent flow,[5,14] and such fluctuations define intracardiac sound-pressure.[5] A linear relation of turbulence to the Reynolds number was demonstrated.[15] A 12 percent decrease in viscosity would increase the Reynolds number 12 percent. Therefore, it is reasonable to assume that the 12 percent decrease in viscosity in subjects with an innocent murmur would increase the turbulence intensity a comparable percentage. Because the fluctuating sound-pressure would be expected to increase as the square of the turbulence intensity,[14] an even greater sound-pressure would result. At the threshold of audibility, the increase in sound-pressure predicted to occur with a 12 percent decrease in viscosity would cause approximately a 2 decibel increase in sound intensity relative to a sound-pressure level of 0.0002 dynes/cm^2. This difference in sound intensity would be detectable with normal hearing.[16] Thus, the increased turbulence calculated to occur due to the lower viscosity in these subjects may contribute to causing the intensity of inaudible ejection murmurs to exceed the threshold of audibility.

Innocent ejection murmurs were traditionally thought to occur distal to the pulmonary valve.[3] However, in adults with normal valves, measurements of intracardiac sound indicate that innocent murmurs

occur in the region of the aortic valve.[17] Studies in dogs support this observation.[17] In adults turbulence is higher in the region of the aortic valve than in that of the pulmonary valve, apparently in relation to the higher blood velocity in the aorta.[18] Irrespective of the site of origin of innocent ejection murmurs, a reduced viscosity of blood would augment disturbances of flow that produce such murmurs.

In conclusion, it appears that a small decrease in blood viscosity, in the presence of a normal hematocrit, may participate in the genesis of innocent ejection murmurs.

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Platelet Function Studies in Coronary Artery Disease

V. Evidence for Enhanced Platelet Microthrombus Formation Activity in Acute Myocardial Infarction

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Circulating platelet microthrombi were evaluated during the acute and convalescent phases of illness in 44 patients admitted to the hospital for chest pain. Similar studies were performed in 10 healthy volunteers and 6 patients with infection. Circulating platelet microthrombi were significantly increased during the acute phase in 22 patients with transmural myocardial infarction compared with values in the other 22 patients without myocardial infarction, the healthy volunteers and the patients with infection alone. This increase in circulating platelet microthrombi declined to normal levels by the 7th hospital day in all but two patients who had evidence of extension of myocardial infarction and died. In contrast, circulating platelet microthrombi were similar in acute and convalescent phases of patients with chest pain but without myocardial infarction and were comparable with values in healthy volunteers. This study suggests that increased circulating platelet microthrombi may be related to tissue necrosis associated with transmural myocardial infarction.

Platelets are thought to be involved in the initiation and propagation of arterial and venous thrombi.[1,2] A new formation of platelet thrombus in a coronary artery has been implicated in the genesis and extension of myocardial infarction.[3–7] Experimental evidence suggests that platelet aggregates may be responsible for occlusion of small coronary and cerebral arteries[3–7] and subsequent ischemia. In 1974, Wu and Hoak[8] first described a technique for measuring in vivo platelet microthrombus formation activity. Some investigators[8–13] later showed evidence for increased platelet microthrombus formation activity in patients with ischemic syndromes, whereas others[14,15] found no such increase. This study was designed to evaluate systematically the platelet microthrombus formation activity in patients with acute myocardial infarction during acute and convalescent phases of tissue damage. Other patients with chest pain but without evidence of myocardial infarction, patients with infection and normal volunteers served as control subjects for comparison.

Methods

Patients: Forty-four men admitted to the cardiac care unit with chest pain were studied. A detailed history was obtained on admission. Serial electrocardiograms and serum enzyme (glutamic oxaloacetic transaminase, lactic dehydrogenase and creatine kinase) determinations were made on three consecutive days. The diagnosis of transmural myocardial infarction was made on the basis of elevation of serum enzyme levels and a history typical of infarction with or without new Q waves or loss of R waves in the electrocardiogram. Ten healthy volunteers (doctors, nurses and medical students) served as control subjects. Six other patients with an infectious process (pharyngitis [two patients], pneumonitis [two patients] and sepsis [two patients]) were also studied for comparison. None of the subjects included had taken aspirin or other drugs known to alter platelet function for 10 days before the study.

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Platelet microthrombus formation activity: Within the first 24 hours (acute phase) and again on the 3rd and 7th days of hospitalization (convalescent phase), blood was drawn from all patients with chest pain to determine in vivo platelet microthrombus formation activity. Blood was drawn only once from all but three healthy volunteers and patients with infection; in these three subjects two samples were drawn 2 hours apart to validate the technique.

The method used to determine microthrombus formation activity was the same as that described by Wu and Hoak.[8] An antecubital vein that had not been previously used was punctured with a large lumen needle (no. 18), and free blood flow was obtained. The first 5 ml of blood was discarded, and samples of exactly 0.5 ml each were drawn into plastic syringes containing 2.0 ml of buffered ethylenediaminetetraacetic acid (EDTA) or EDTA and formalin. The samples were taken in duplicate, gently tilted and allowed to stand for 15 minutes at room temperature. The four tubes were then centrifuged simultaneously for 8 minutes at 150 *g* to obtain platelet-rich plasma (PRP). Platelet counts on both platelet-rich plasma samples were determined under phase microscopy within 1 hour of blood collecion. The results were expressed as follows: Microthrombus index = platelet count in EDTA-formalin PRP/platelet count in EDTA PRP.

This method is based on the concept that, when present, platelet aggregates will be fixed in the EDTA-formalin mixture and centrifuged down. Therefore, the platelet count of the platelet-rich plasma solution will be reduced. However, in the syringe with EDTA alone, platelet aggregates are broken. Therefore, the ratio of platelet count in the two samples approaches 1 when there are no aggregates but drops below 1 if aggregates are present.

The average of the duplicate values was used to calculate the mean and the standard error. Student's *t* test was used for statistical calculations. A probability (*P*) value of <0.05 was considered statistically significant.

Results

Patients with chest pain: The criteria for myocardial infarction were met in 22 of the 44 patients admitted with chest pain, but were not met in the other patients. The age of all patients studied ranged from 44 to 68 years. The mean age of the patients with myocardial infarction (54 years) was similar to that of the patients without infarction (53 years). The normal volunteers and patients with infection alone had a mean age of 31 and 52 years, respectively. There was no significant difference in the prevalence of diabetes mellitus, hypertension, hyperlipidemia or smoking among the different groups of subjects. Nine of the 22 patients with myocardial infarction had an anterior wall infarction and 13 an inferoposterior wall infarction. Myocardial ischemia was suspected clinically in 12 of the 22 patients without myocardial infarction.

All 22 patients without and 20 of the 22 patients with myocardial infarction had an uneventful course of hospitalization. Two patients with infarction had evidence (additional chest pain, electrocardiographic changes and enzyme elevation after the initial diagnosis) of extension of the infarction on about the 7th hospital day. Both of these patients died.

Microthrombus index in patients with chest pain: *Acute phase:* The duplicate values obtained in each patient agreed very closely (mean variation 0.04). The microthrombus index in patients with myocardial infarction ranged from 0.24 to 0.92 (mean ± standard error of the mean, 0.62 ± 0.03) and in those without infarction from 0.64 to 1.10 (mean 0.89 ± 0.02) (Fig. 1).

During the acute phase, the microthrombus index was significantly lower ($P < 0.01$) in patients with myocardial infarction than in patients without infarction. The mean values were similar in patients with anterior (0.64 ± 0.04) and inferoposterior (0.61 ± 0.04) wall infarction.

Convalescent phase: In all but two patients with myocardial infarction the microthrombus index increased during the convalescent phase. On the 3rd hospital day, the mean index was 0.70 ± 0.05; on the 7th hospital day it had increased to 0.79 ± 0.04 (anterior wall infarction 0.77 ± 0.08, inferoposterior wall infarction 0.82 ± 0.04, both $P < 0.01$). Two patients with anterior wall infarction had clinical and laboratory evidence of extension of myocardial infarction. In both patients the microthrombus index decreased on the 7th hospital day (from 0.41 to 0.22 in one and from 0.78 to 0.59 in the other). In contrast, in patients without myocardial infarction, the microthrombus index was unchanged from the value in the acute phase on the 3rd (0.89 ± 0.03) and 7th (0.87 ± 0.03) hospital days. The index on the 7th day was similar in the patient groups with and without myocardial infarction (Fig. 2).

Among patients without myocardial infarction, the microthrombus index in subjects clinically thought to have myocardial ischemia (mean 0.87 ± 0.03) was similar to that in patients with a nonischemic chest pain syndrome (mean 0.90 ± 0.04).

Microthrombus index in healthy volunteers: In this group, the microthrombus index ranged from 0.86 to 1.02 (mean 0.94 ± 0.02) and repeat determinations 2 hours later in three volunteers were also similar (mean variation, 0.03). The mean value for the microthrombus index in patients with myocardial infarction was lower ($P < 0.001$) than that in healthy volunteers during the acute phase, but values in the two groups were similar on the 7th hospital day. In patients with chest pain but without myocardial infarction, the microthrombus index was similar to that in the healthy volunteers in both the acute and convalescent phases.

Microthrombus index in patients with infection: In patients with infection alone, the index ranged from 0.85 to 0.91 (mean 0.89 ± 0.01). This value was similar to that in both healthy volunteers and patients with chest pain without myocardial infarction but was higher ($P < 0.01$) than that in patients with chest pain and infarction.

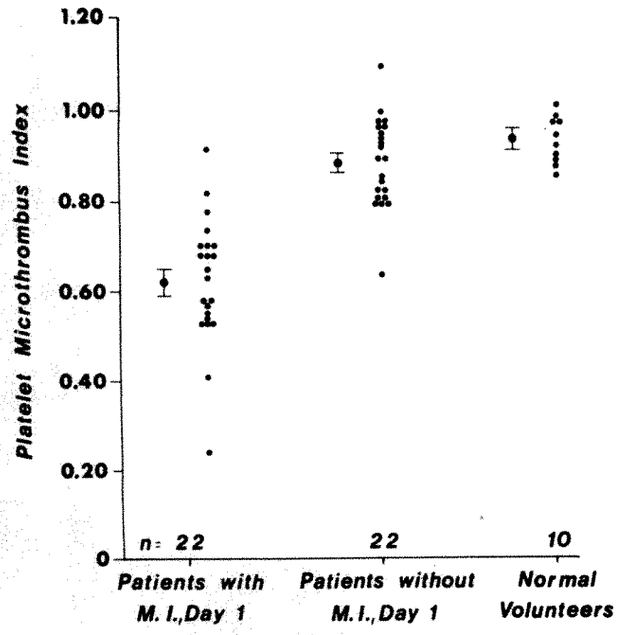


FIGURE 1. Platelet microthrombus index in patients with and without myocardial infarction (M.I.) on the 1st hospital day, and in normal volunteers. The mean index was significantly lower ($P < 0.01$) in patients with myocardial infarction than in the other two groups. n = number of patients.

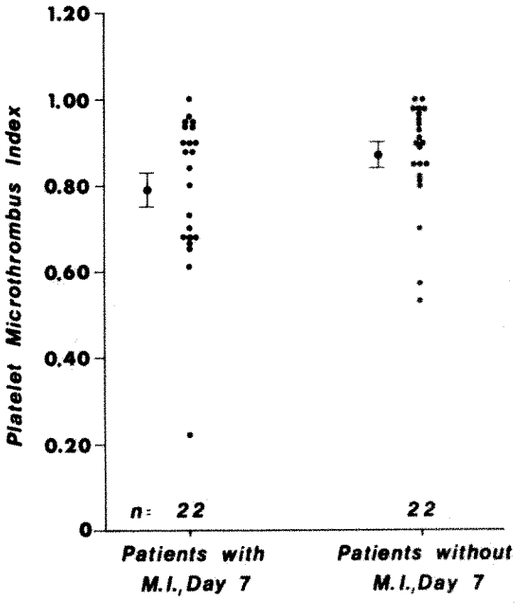


FIGURE 2. Platelet microthrombus index on the 7th hospital day in patients with and without myocardial infarction (M.I.). The mean index was similar in the two patient groups.

Discussion

Several investigators[16–20] have noted platelet hyperaggregability in patients with myocardial ischemia and infarction. The observation[6,7] of platelet aggregates in the coronary vessels of patients dying suddenly also suggests a role for platelets in coronary death. As platelets come in contact with collagen in the atherosclerotic arteries, release of platelet aggregation stimulant and vasoconstrictor thromboxane A_2 may occur.[21,22] Platelet aggregates thus formed could occlude the atherosclerotic vasculature, leading to ischemia and tissue injury.[23,24] In acute myocardial ischemia and infarction the associated release of adenosine diphosphate, serotonin and catecholamine could also lead to further platelet aggregation, resulting in occlusion of the microcirculation with platelet thrombi.[2] Recently, elevation of platelet factor IV during the acute phase of myocardial infarction has been demonstrated, further suggesting a relation between myocardial damage and platelet activation.[25]

Association of increased platelet microthrombi and myocardial infarction: Using the technique for measuring in vivo platelet aggregate formation activity,[8] we found that acute transmural myocardial infarction is associated with an increase in circulating platelet microthrombi. This platelet microthrombi formation activity is equally increased in patients with anterior and inferoposterior wall myocardial infarction in the acute phase. The level gradually declines to normal by the 7th hospital day in patients with an uncomplicated course. However, a persistently high activity or a further increase in circulating platelet microthrombi is suggestive of continued myocardial damage. In contrast to patients with myocardial infarction, patients hospitalized with chest pain without evidence of myocardial damage and patients with infection without tissue damage do not have a similar increase in platelet microthrombi formation activity.

Our observations of increased platelet microthrombi in patients with myocardial damage are in agreement with those of some previous studies.[8,11–13] Others[14,15] failed to show a similar increase in patients with myocardial infarction. In some of the latter studies,[14] the test for circulating platelet microthrombi was performed late in the course of infarction, and an elevation occurring early in the course may have thus been missed. In other studies,[15] the type of myocardial injury—that is, subendocardial ischemia or transmural infarction—was not specified. Our studies and those of Wu and Hoak[8] and Guyton and Willerson[13] suggest that platelet aggregate formation activity is increased only in those patients with chest pain who have a myocardial infarction. These observations imply an association of increased platelet microthrombus formation activity either in the genesis or as a result of tissue injury, as proposed by Dougherty et al.[10]

We[26] and others[9,10] also demonstrated an increase in circulating platelet microthrombi in other vasoocclusive phenomena associated with tissue damage. The normal levels of circulating platelet microthrombi in patients with infection without tissue damage as observed in our study further suggests an important role of increased microthombus formation activity in tissue damage.

Platelet microthrombi and myocardial ischemia: If platelet hyperaggregability is a factor in the initiation of ischemia, one would anticipate an increase in platelet

microthrombi in patients with myocardial ischemia as well. However, in our patients with ischemic chest pain without tissue damage, absence of such an increase may be due to several factors. It is possible that the increase in platelet microthrombus formation activity occurs only transiently and initiates ischemia by compromising blood flow. Further platelet activation may be on the basis of myocardial tissue damage. Thus, increased platelet microthrombus formation may not be detected in the peripheral venous blood unless the blood is drawn just before the ischemic event or tissue damage. It is also likely that the test for quantitating platelet microthrombi in the peripheral venous blood is not sensitive enough to detect minor but significant changes occurring in the coronary arteries.

Implications: The technique for measuring circulating platelet microthrombi used in our study is simple and reproducible if the blood samples are studied within 1 hour of being drawn.[9–13] The microthrombus index is not affected by age, sex, smoking, fatty foods, physical exertion or drugs such as anticoagulant agents.[13–15] Because we did not study in vivo platelet microthrombus formation activity before evolution of tissue necrosis in patients with myocardial infarction, its role in the genesis of myocardial damage remains speculative. Nevertheless, the increase in circulating platelet aggregates appears to be related to tissue damage associated with vascular occlusion. Further studies are warranted to define the exact role of platelet aggregate formation in tissue ischemia, necrosis and recovery.

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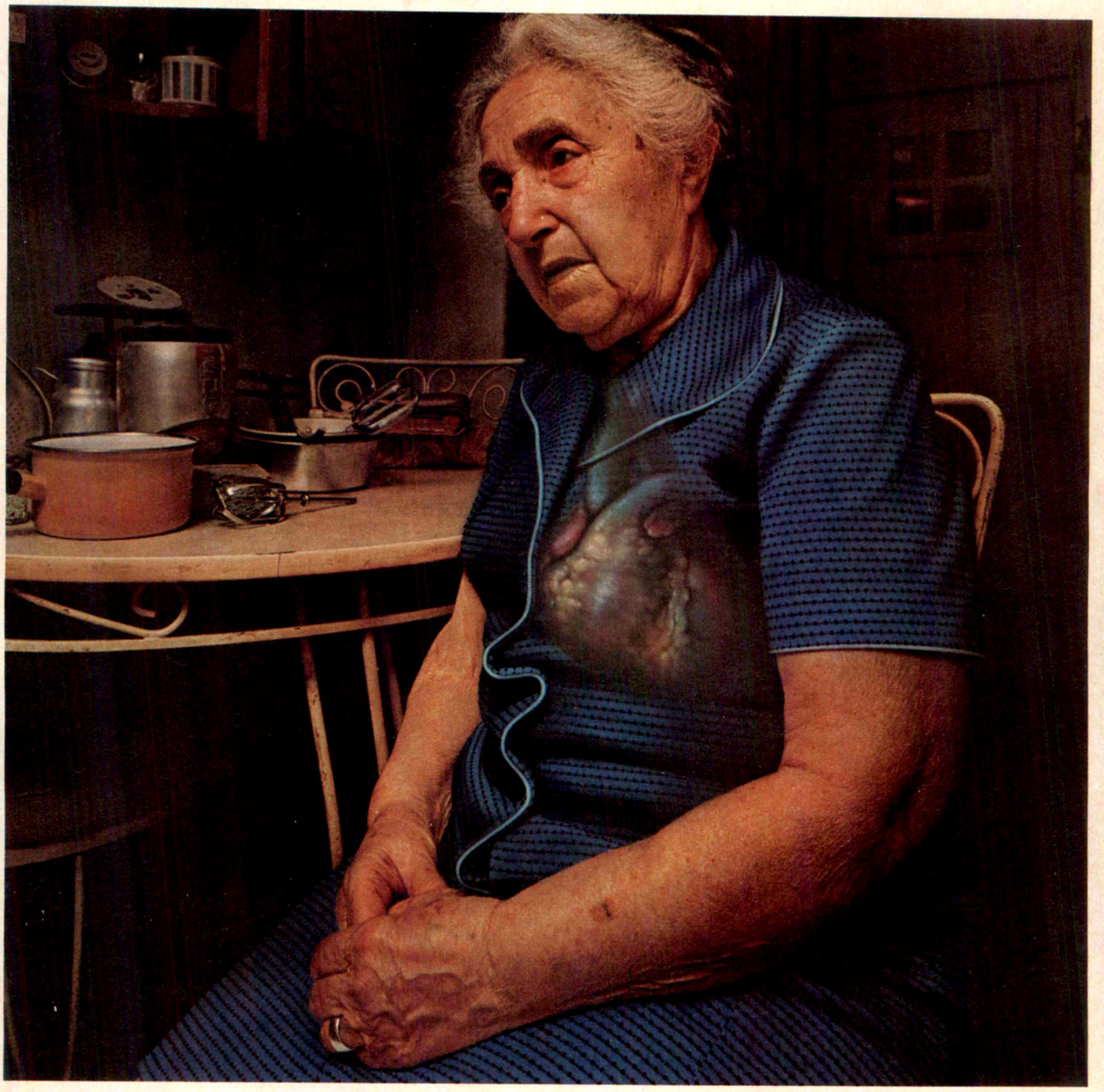
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There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

Precautions: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when

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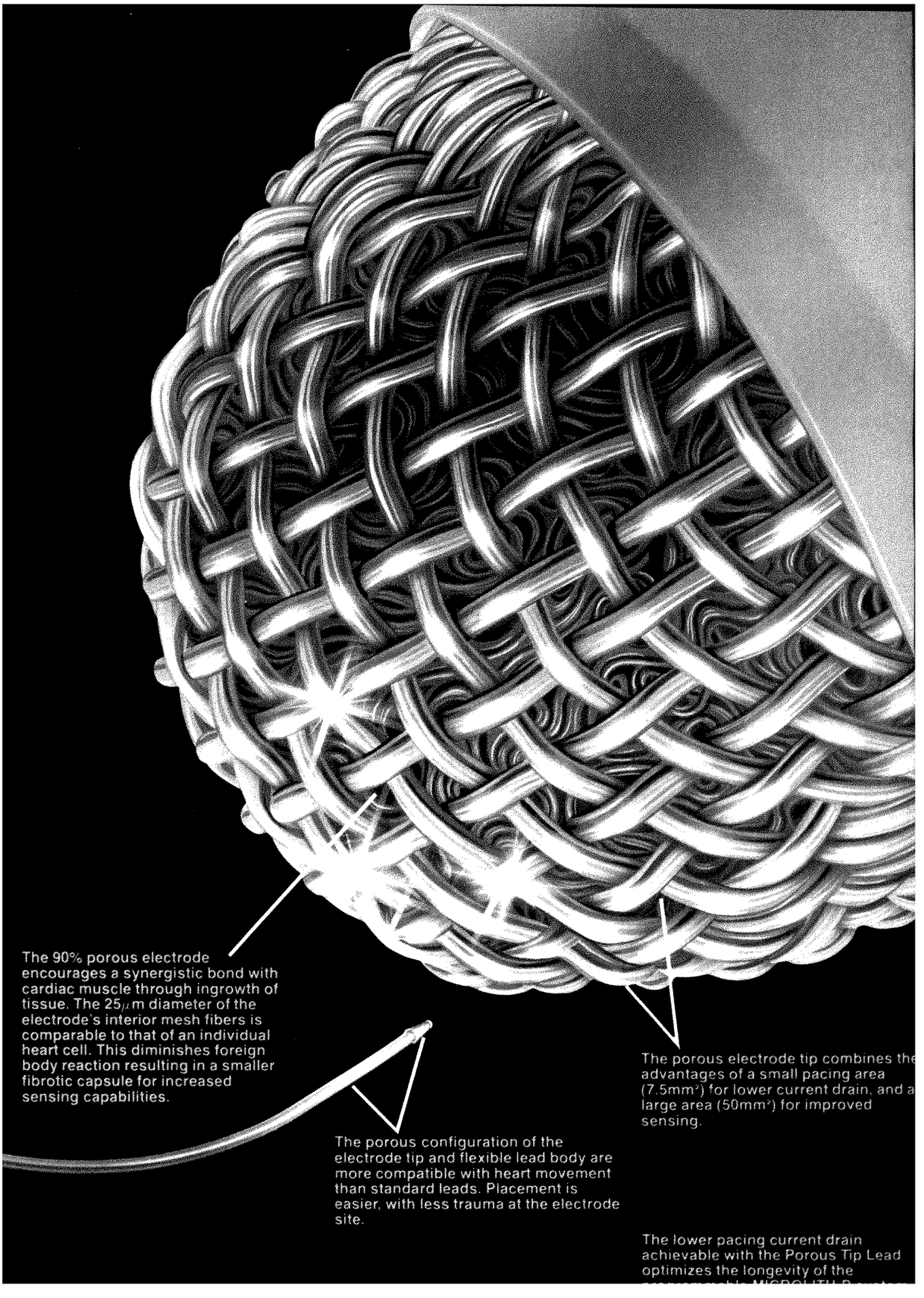
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Less critical, but important in fostering patient compliance with maintenance therapy, patients treated with 'Dyazide' seldom develop hypokalemia, often a factor in patients' decisions to abandon maintenance therapy because of muscle cramps, fatigue, and malaise.

Avoids Development of Tolerance

As the hydrochlorothiazide in 'Dyazide' exerts its diuretic effect, 'Dyrenium' not only enhances fluid output, it blocks distal reabsorptive mechanisms stimulated by compensatory elevation of aldosterone. Even during extended maintenance therapy, drug tolerance is avoided.

Serum K^+ and BUN should be checked periodically. (See warnings.)

'Dyazide' can cause hyperkalemia, though it is rare in patients with normal renal function. Serum K^+ and BUN should be checked periodically, particularly in elderly, diabetics, and those with suspected or confirmed renal insufficiency. Potassium supplements should not be used unless hypokalemia develops or dietary K^+ intake is markedly impaired. Not for initial therapy (see box warning).

See next page for brief summary of prescribing information.

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Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Potassium-Sparing Diuretic*

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Preexisting elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

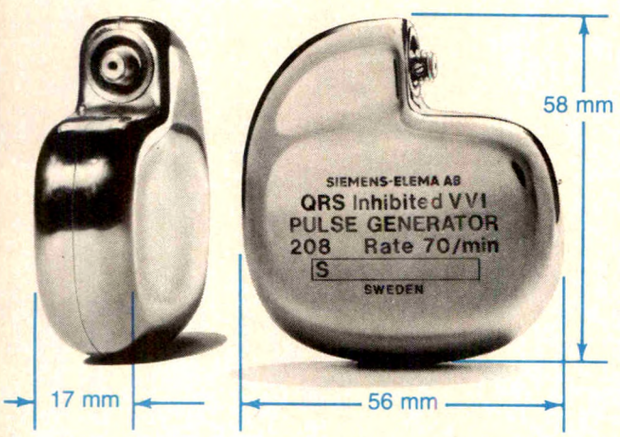
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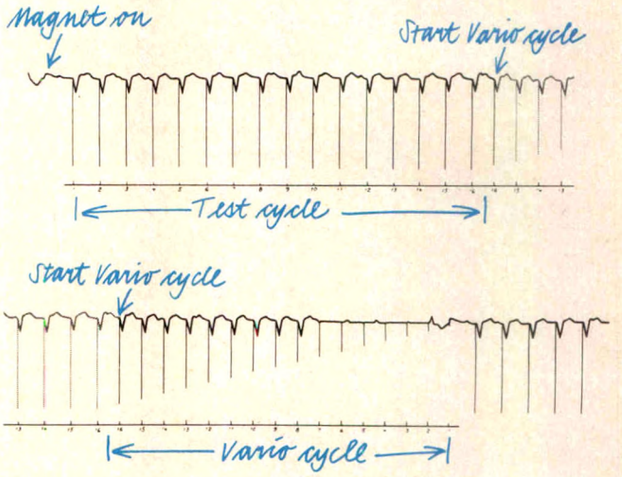
Dr. Rune Elmqvist of Siemens-Elema and Dr. Ake Senning developed the pulse generator implanted by Dr. Senning in 1958 for the world's first pacemaker implantation.

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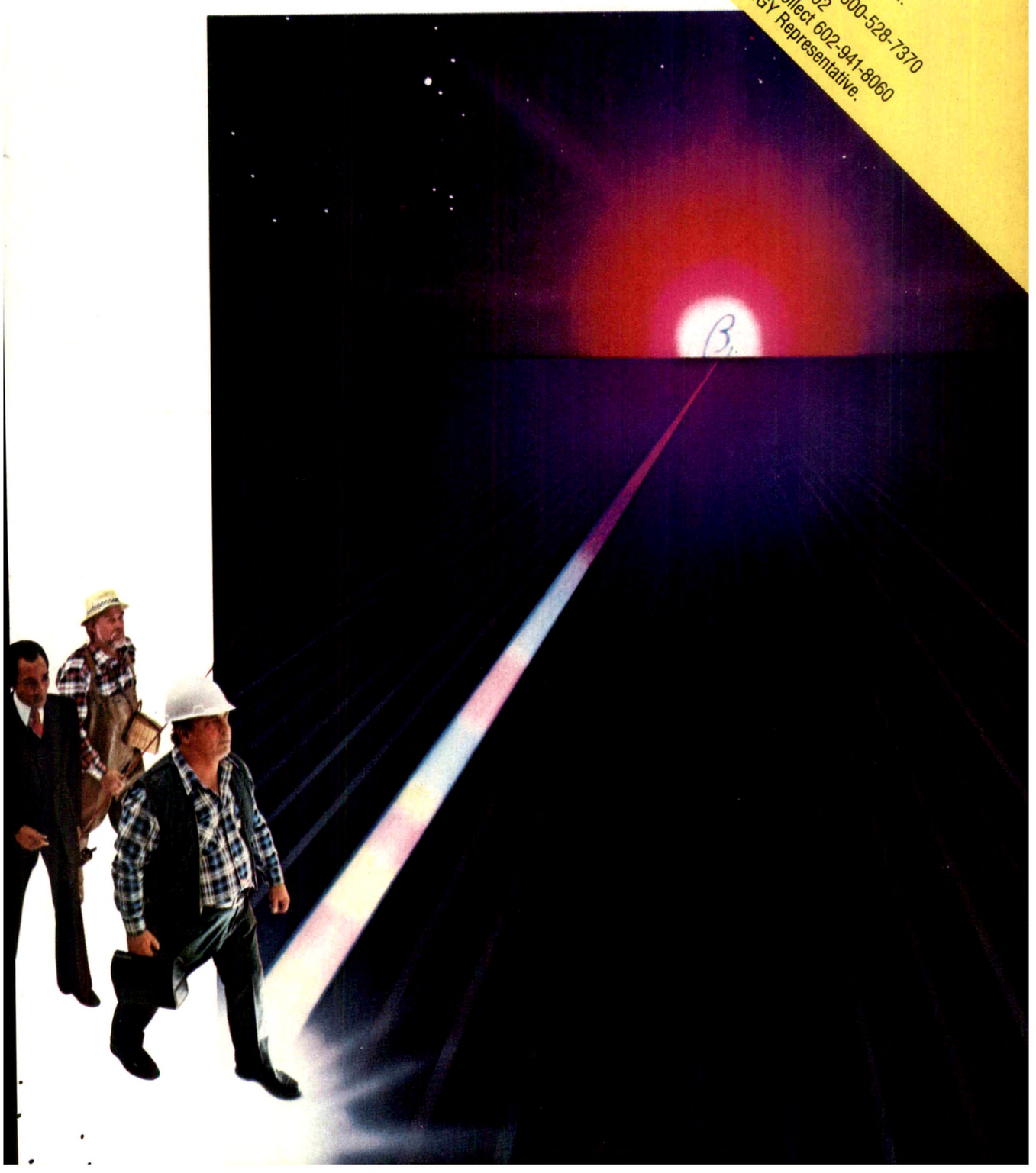
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Does not interfere with sex life of patients.

Lopressor usually does not cause impotence or loss of libido, complaints which many male patients encounter with sympathetic inhibitors, but which they may be reluctant to discuss with their physicians.

Rarely causes daytime sedation or postural hypotension.

Most of the side effects that have occurred with Lopressor are mild and transient. For example, tiredness and dizziness occur in about 10% of patients; depression, diarrhea in about 5%. Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt heart failure.

Easy to take twice-a-day dosage.

Patients will also appreciate the easy-to-remember b.i.d. dosage of Lopressor. Since b.i.d. dosage is known to encourage patient adherence, this is another way that Lopressor improves your chances for long-term therapeutic success.

Significantly reduces blood pressure when added to a diuretic.

Lopressor caused a significant fall in blood pressure when given to patients already receiving a diuretic. Investigators reporting in the British Journal of Pharmacology concluded that "Metoprolol in combination with chlorthalidone appears to be an effective and well-tolerated treatment for mild and moderate hypertension in those patients not responding to chlorthalidone alone."*

Treatment Period

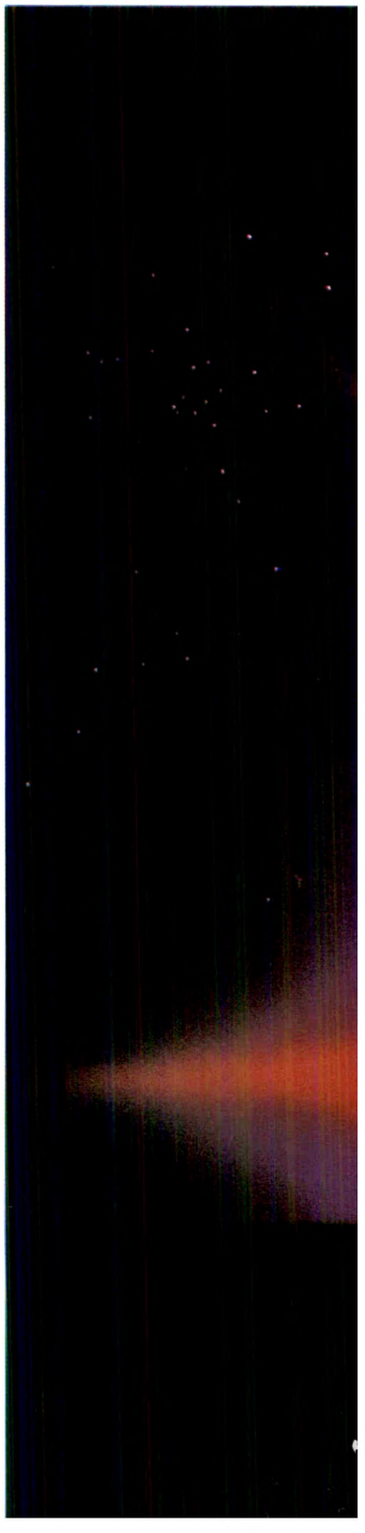
Placebo + chlorthalidone		Metoprolol + chlorthalidone
one month		
Systolic BP (mmHg)		
158±4	supine	142±4
160±5	standing	147±3
Diastolic BP (mmHg)		
96±2	supine	87±1
102±2	standing	94±1
two months		
Systolic BP (mmHg)		
159±4	supine	146±4
159±4	standing	147±4
Diastolic BP (mmHg)		
96±2	supine	89±1
101±2	standing	95±1
three months		
Systolic BP (mmHg)		
158±5	supine	148±3
159±4	standing	149±3
Diastolic BP (mmHg)		
97±2	supine	87±1
101±2	standing	93±1

Works primarily where it should... not where it shouldn't.

Lopressor is the only relatively selective beta blocker available in the United States. Unlike the first generation beta blocker, propranolol, which is nonselective, Lopressor has a preferential effect on beta receptors involved in lowering blood pressure. It has less effect on beta receptors that do not relate to antihypertensive mechanisms.

Please see last page of this advertisement for brief summary of prescribing information.

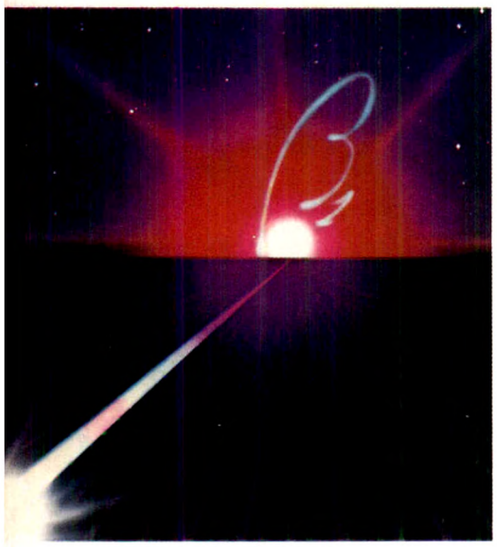
*Jäättelä A, Pyörälä K: A controlled study on the antihypertensive effect of a new β-adrenergic receptor blocking drug, metoprolol, in combination with chlorthalidone. Br J Pharmacol 3:655-660, 1976.





The relatively selective beta blocker for hypertension.

Lopressor™
metoprolol tartrate



Lopressor™
brand of
metoprolol tartrate

An antihypertensive beta-blocking agent

Indications Lopressor, brand of metoprolol tartrate, is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor, brand of metoprolol tartrate, is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor, brand of metoprolol tartrate, should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor, brand of metoprolol tartrate, therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor, brand of metoprolol tartrate, should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor, brand of metoprolol tartrate, may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in three doses daily, instead of two, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor, brand of metoprolol tartrate, should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor, brand of metoprolol tartrate, plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor, brand of metoprolol tartrate, should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, Raynaud's disease, palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor, brand of metoprolol tartrate, during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor, brand of metoprolol tartrate, should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor, brand of metoprolol tartrate, is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

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A Biologic Model of Parasystole

JOSE JALIFE, MD
GORDON K. MOE, MD, PhD, FACC

Utica, New York

The electrotonic interactions of a parasystolic pacemaker with ventricular responses to the normal pacemaker across an area of depressed excitability were simulated in a model consisting of strands of canine Purkinje fibers mounted in a sucrose gap preparation. Experiments were conducted to study the patterns of ectopic activity that result from entrainment of the "ectopic" pacemaker (EP) on one side of the sucrose gap by evoked responses (SN) on the other side of the gap. When one-way conduction ("entrance block") was established, manipulations of the SN frequency and of the impedance between the two outer chambers resulted in periods of silence, concealed or manifest bigeminy, trigeminy and quadrigeminy, and periods of more complex patterns of group beating as the entrainment ratios changed. The results confirm the predictions of the previously described mathematical model that these patterns depend on the magnitude of the electrotonic influence of SN on the EP cycle length and also on the ratio of the intrinsic frequencies. These studies should help to distinguish between reentrant and parasystolic mechanisms in clinical arrhythmias.

Brief subthreshold depolarizations induced during the first half of the cycle of a spontaneous pacemaker delay the subsequent discharge of the pacemaker.[1,2] Depolarizations of similar duration and magnitude induced late in the cycle accelerate the subsequent discharge. This biphasic influence, studied in a three chamber sucrose gap preparation of canine false tendon, was similar whether the depolarization was induced by current pulses or by spontaneous or evoked action potentials across the gap.[2] The results suggest that a parasystolic focus protected but not insulated by an area of depressed excitability may be modulated by electrical events in the surrounding tissue; the spontaneous cycle length may be prolonged or abbreviated depending on the timing of the electrotonic influence.

In a recent investigation, the interactions between two pacemakers were simulated in a computer model.[3] An ectopic pacemaker (EP), protected but not completely insulated from ventricular responses to the primary (sinoatrial) S-A nodal pacemaker (SN), was programmed to respond along a biphasic curve of interaction similar to that observed in isolated tissue. Computer runs covered wide ranges of SN frequencies at several amplitudes of the simulated electrotonic influence. Wide phases of entrainment of the ectopic pacemaker at 1:1, 2:1 or higher ratios resulted. There were phases of "parasystolic" rhythms with variable coupling intervals, periods of fixed coupling with concealed or manifest ectopic activity, and periods of silence in which no ectopic activity was manifest. The resulting patterns shifted in mathematically obligatory ways as the relation between the two frequencies was altered.

The results obtained in the computer model were applied to clinical examples of arrhythmias attributed to either ectopic pacemaker activity

From the Masonic Medical Research Laboratory, Utica, New York. This study was supported in part by Grant HL 19487 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received August 2, 1978; revised manuscript received October 11, 1978, accepted October 12, 1978.

Address for reprints: Jose Jalife, MD, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, New York 13503.

("true" parasystole) or to reentry ("extrasystolic" rhythms). The analysis of many published electrocardiograms revealed a remarkable similarity to the behavior of the computer model, suggesting that many patterns of arrhythmias ascribed to reentrant mechanisms can be generated by a parasystolic focus.

The mathematically obligatory rules that emerged from this study suggested additional tests in the biologic model. In this study, these tests were conducted in canine Purkinje fibers mounted in the sucrose gap chamber. The evidence obtained from the mathematical model[3] was applied to the study of the entrainment of a spontaneous pacemaker (EP) on one side of the area of block (the sucrose gap) by a stimulated fiber segment across the gap in the ranges of 1:1, 2:1 and 3:1 entrainment. Manipulations of the "SN" frequency and of the impedance between the two outer chambers resulted in periods of silence, concealed and manifest bigeminy, trigeminy and quadrigeminy, and periods of complex but predictable patterns as the entrainment ratios shifted from one level to another.

Methods

Experimental model: The methods were similar to those described earlier.[2] Unbranched free-running false tendons, excised from dog hearts, were placed in a three-chambered tissue bath (Fig. 1). Spontaneous pacemaker activity was induced in the segment of fiber in chamber 1 ("ectopic" pacemaker [EP]) by superfusion with Tyrode's solution containing a reduced concentration of potassium (2 mM) plus epinephrine, 0.1 μg/ml. Chamber 2, with a length of 1 mm, was perfused with a solution containing sucrose (300 mM) and dextrose (5 mM) to replace the ions of the extracell space and thus provide an area of conduction block; calcium chloride (0.1 mM) was added to the solution to prevent cell uncoupling.[4] In all experiments, chamber 3 ("sinus node" [SN]) was perfused with Tyrode's solution containing 4 mM potassium chloride.

The preparations were positioned asymmetrically across the three chambers in such a way that the fiber segment in chamber 1 was longer than that in chamber 3. With this arrangement, only electrotonic propagation occurred from chamber 3 to chamber 1, but full action potential propagation occurred in the opposite direction; that is, unidirectional block was achieved. Except where otherwise noted, interaction patterns between the fiber segments EP and SN were studied by applying rhythmic stimuli 1 msec in duration and of twice threshold strength to the SN segment at various frequencies, while the EP segment was allowed to beat spontaneously. Transmembrane potentials were recorded as previously described.[2] For clarity, action potentials that overlap on the original film were projected and traced in all illustrations except Figures 11 and 12.

To modulate the degree of block between EP and SN, an external shunt pathway with a variable resistor (200 kilo-ohms), was connected to coiled silver-silver chloride electrodes immersed in the two outer chambers. In three experiments, the upstroke of the action potential from EP was used to activate an electronic switch connected in parallel with the variable resistor. When the switch was in the "on" position it provided a shunt of 2800 ohms between the chambers for a variable interval and allowed action potentials to propagate. In this manner, propagation from EP to SN was facilitated, whereas only electrotonic potentials propagated in the opposite direction.

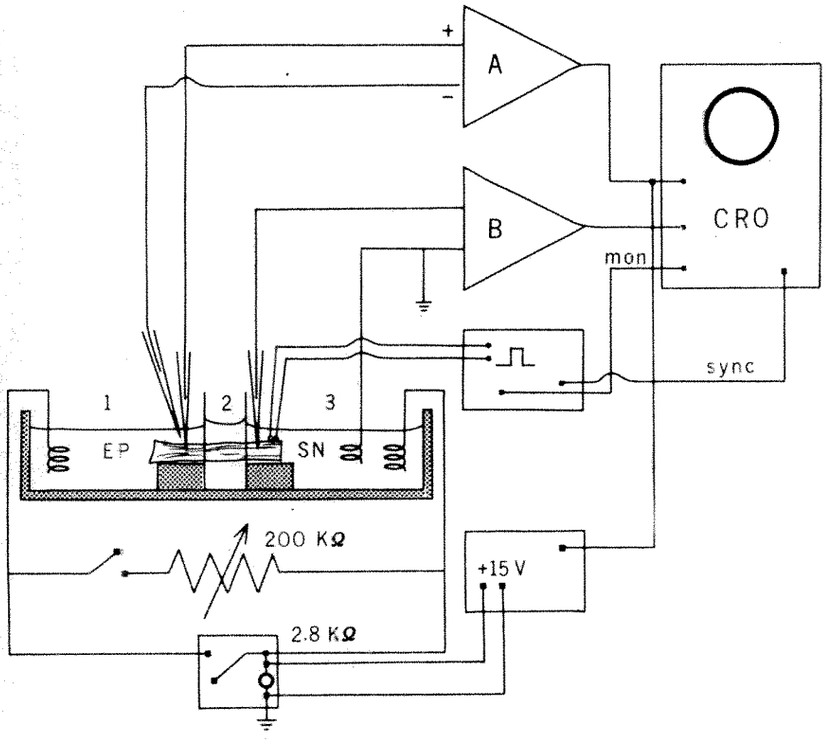


FIGURE 1. Experimental set up. A = differential microelectrode amplifier recording activity from EP (chamber 1). B = single ended amplifier recording from SN (chamber 3). Chamber 2 is the sucrose gap. CRO = cathode ray oscilloscope; mon = stimulus monitor; sync = oscilloscope synchronizing signal. Chambers 1 and 3 could be shunted with a variable resistor (200 kilo-ohms) connected to coiled silver-silver chloride electrodes. In some experiments the output from A was used to trigger a +15 volt signal of variable duration to activate an electronic switch. In the "on" position the switch provided a complete shunt (2.8 kilo-ohms) between chambers 1 and 3.

Definitions: *Intrinsic EP/SN ratio:* the ratio of the unmodulated, free-running ectopic cycle length to the driven cycle length of SN.

Operative EP/SN ratio: the ratio of the average actual EP cycle to the driven SN cycle. The ratio EP/SN is the same as SN/EP frequency.

Entrainment ratio: the same as the operative SN/EP frequency ratio, that is, the number of *stimuli* applied to SN divided by the number of *actual* discharges of EP within a given time period. In a bigeminal rhythm, for example, an "ectopic" response follows every driven response, but the entrainment ratio is 2:1 if a compensatory pause is allowed; every second stimulus (like every second P wave in a clinical example) would be blocked by interference. A 2:1 entrainment ratio can yield a 4:1 ratio of *manifest* ectopic activity; that is, every second ectopic discharge is "concealed."

Periodicity: the development of repetitive patterns. For example, a pattern of alternate (manifest) bigeminy and trigeminy may represent 5:2 entrainment and will repeat itself every sixth response.

Results

"Entrance" Block and Parasystole

To explain the protection of an ectopic pacemaker from propagated activity in surrounding ventricular tissue, it is necessary to assume unidirectional block ("entrance" block) between the two tissues. Protection need not be complete. The pacemaker frequency can be modulated by local circuit currents from the surrounding tissues and still manifest itself as parasystolic. Figure 2 illustrates an experimental demonstration of this interaction. Two pacemakers were allowed to interact across an area of "entrance" block provided by the sucrose gap. In all panels the upper tracing shows transmembrane potentials recorded from SN. Lower tracings were recorded from the spontaneous pacemaker, EP. The same impalements were maintained in panels A, B and C.

Panel A of Figure 2 was recorded to illustrate the interaction of two spontaneously active pacemakers across the area of conduction block. No stimuli were applied to either of the two active chambers. The average spontaneous EP cycle length was 1,297 msec; the spontaneous cycle length of the fiber beyond the gap was much longer, and a 3:1 conduction block from EP to SN was present. As the membrane potential of the SN fiber gradually approached threshold, the amplitude of the electrotonic potentials accompanying the EP discharges increased progressively. These changes reflect the progressive increase of membrane resistance during the slow diastolic depolarization of SN. When the electrotonic potential induced in SN by the third EP discharge reached threshold, SN fired an action potential that occurred 280 msec after EP, or at 22 percent of the EP pacemaker cycle. The electrotonic effect of the SN discharge, occurring early in the EP cycle, was a delaying one; the EP cycle length was increased by 3.7 percent to 1,345 msec. At the time of the fourth and fifth EP discharges, the SN membrane resistance was low, the electrotonic potentials did not reach threshold, SN did not fire, and the EP cycle length resumed its intrinsic value.

Panel B of Figure 2 was recorded to illustrate that a reduction of the impedance between the two chambers can controllably reduce the degree of block; in this case, from 3:1 "exit" block (panel A) to 1:1 transmission (panel B). At the arrow a 30 kilo-ohm shunt was switched in to bridge the sucrose gap. A significant increase of the EP cycle length always accompanied this maneuver. An accurate estimate of the "intrinsic" cycle length of EP is no longer possible; however, when SN occurs very early, as in the second EP cycle, the electrotonic influence is very small, and therefore a reasonably close approximation can be made (1,375 msec). The greater delay attending the propagation of subsequent responses in panel B resulted in some prolongation of the EP cycles to 1,465 msec. The clinical counterpart of this simulation would be a slow idioventricular rhythm with first degree exit block between the ectopic pacemaker and the ventricle.

Panel C of Figure 2 illustrates one of the characteristic response patterns of the model when SN, no longer allowed to respond spontaneously, was driven at a fixed frequency simulating ventricular responses to a supraventricular pacemaker. The same shunt resistance as in panel B was maintained, and unidirectional block was achieved. Propagation from EP to SN occurred whenever SN was excitable. Propagation from SN to EP did not occur, but electrotonic interactions were always present, appearing as alterations in the EP transmembrane potentials and as modulations of the EP cycle length. At the driven SN cycle length of 1,000 msec, the *intrinsic* ratio of EP/SN cycles was 1,375/1,000, or 1.375. Modulation of the EP cycles yielded a "parasystolic" pattern of premature, interpolated and fusion beats, with a repeating period of 14:10. The coupling intervals manifest in the SN record were 920 msec for the premature response (P) (which is followed by a compensatory pause), 460 msec for the interpolated response (I) and 985 msec for the "fusion" beat (F).

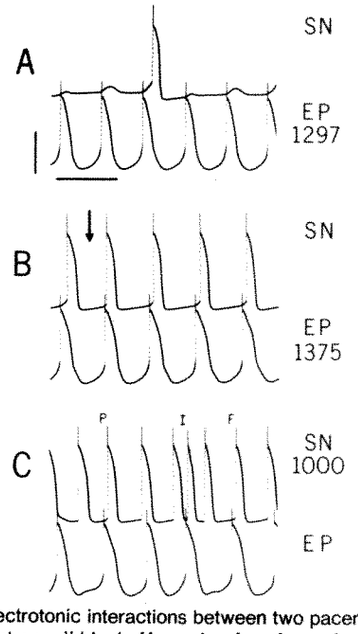


FIGURE 2. Electrotonic interactions between two pacemakers across an area of "entrance" block. **Upper tracings in each panel** were recorded from chamber 3 (SN), **lower tracings** from chamber 1 (EP). **Panel A,** 15 minutes of sucrose perfusion. In **panel B,** a 30,000 ohm resistor was connected into the circuit at the moment indicated by the **arrow.** In **panel C,** SN was driven at a cycle length of 1,000 msec. The numbers indicate the cycle length in msec. Transmembrane potentials were traced from projections of the original records. Calibrations are 50 mv and 2,000 msec. F = fusion beat; I = interpolated beat; P = premature beat.

The interectopic intervals P-I and I-F, which clearly encompass two and one EP cycles, respectively, are in the ratio of 1.67, not 2.0. The reasons for this departure from "classic" parasystolic behavior are apparent in the recorded cycles of EP. The intermediate SN discharge in the first EP cycle, occurring at 52 percent of its intrinsic cycle, delayed the EP discharge. The net effect of the two intervening SN responses in the second EP cycle was abbreviation. The single intervening SN response in the third cycle caused still greater abbreviation, and the two intervening SN responses in the fourth cycle caused prolongation. Although the average EP cycle during this episode was about 1,400 msec, the modulated cycles ranged from 1,220 to 1,470 msec.The variations in EP cycle length were not random but were mandated by the biphasic electrotonic influence on the pacemaker. Modulation of the intrinsic cycle (1,375 msec) within a range of about ±10 percent depended reproducibly on the position of the SN discharges within the EP cycle.

The example of parasystolic interaction shown in Figure 2 was chosen to illustrate the wide variations of coupling interval that are characteristic of classic parasystole; the amplitude of the electrotonic influence was only ±10 percent. At greater amplitudes, the entrained variations of EP cycle length increase, and the coupling intervals become constrained within narrower limits.

The periodic pattern displayed in Figure 2C was maintained as long as the conditions were held constant. Slight variations in either the impedance between the chambers or in the SN driving frequency altered the pattern, but the alteration was always predictable, that is, in strict conformity with the rules of the mathematical model.

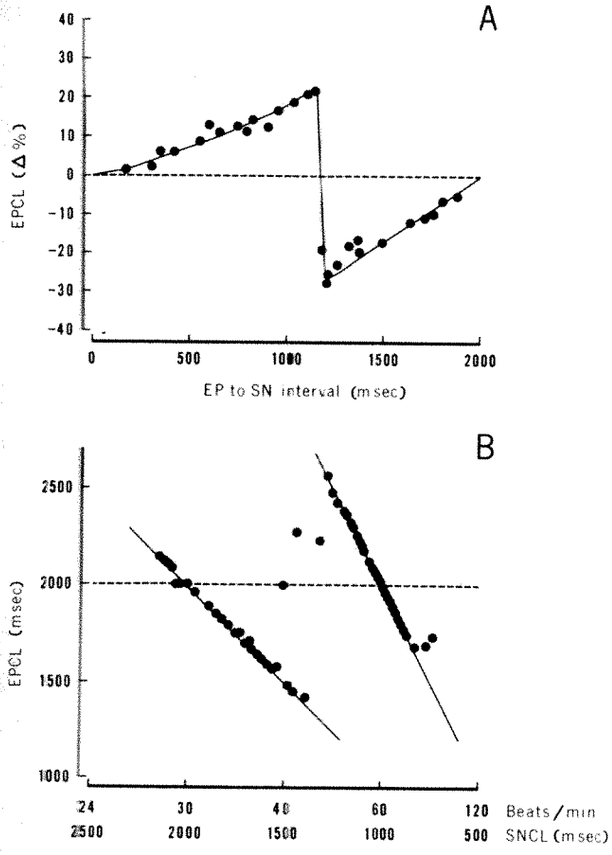


FIGURE 3. Biphasic influence and electrotonically mediated entrainment of a pacemaker (EP) by driven responses (SN) across an area of block. **Panel A** shows the percentage change of the spontaneous EP cycle length (EPCL) (**ordinate**) as a function of the interval of SN with respect to the last EP discharge (**abscissa**), expressed in msec. The **broken line** represents no change in EP cycle length. Delay of EP occurs when SN arrives early in the EP cycle; acceleration occurs when it arrives late in the cycle. **Panel B** illustrates the entrainment of EP by periodic SN driven discharges as a function of the driving frequency. The **ordinate** represents the EP cycle length expressed in msec, and the **abscissa** the SN frequency (beats/min) and respective SN cycle lengths (SNCL) in msec. Entrainment is shown at the levels of 1:1 and 2:1. The **broken** line represents the relation that would exist if the two pacemakers were completely independent.

Entrainment

In the biologic model, as in the mathematical model, an "ectopic" pacemaker can be entrained within wide ranges both above and below its intrinsic frequency. Figure 3 illustrates an example of electrotonically mediated entrainment in one of five such experiments. The degree of electrotonic modulation, recorded as a function of the temporal position of stimulated SN responses in the pacemaker cycle, is plotted in Figure 3A; the entrainment of EP as a function of the driving frequency in the same preparation is illustrated in Figure 3B.

The biphasic curve of Figure 3A was obtained in the same way as in earlier descriptions.[2,3] After a stable series of spontaneous cycles of EP, a single response of SN was initiated at various intervals in the pacemaker cycle, and the resulting delay or acceleration of the next discharge of EP was recorded as a percentage, plus or minus, of the average unmodulated cycle of 2,000 msec. Stimuli to SN early in the EP cycle delayed the ensuing response of EP, up to a maximum of about 21 percent. After a sharp reversal at 60 percent of the EP cycle (1,200 msec), evoked responses of SN accelerated the next discharge by more than 25 percent.

The entrainment of EP that resulted from this electrotonic interaction was studied by allowing EP to fire spontaneously while the SN segment in chamber 3 was driven at cycle lengths of 740 to 2,140 msec, in steps of 50 msec or less. At each driven cycle length, responses were recorded until a stable rhythmic pattern was established, after which the intrinsic EP cycle was again recorded in the absence of driven responses.

Entrainment of the pacemaker is apparent in Figure 3B as deviations from the horizontal broken line defining the intrinsic cycle of 2,000 msec. Entrainment at 1:1 is defined by the line of unit slope extending from a driven cycle length of 2,140 msec (*slower* than the intrinsic frequency) to about 1,400. At a frequency dictated by the reversal point in panel A, there is a phase of instability, followed by a stable phase of entrainment at 2:1, extending from the driven cycle of 1,280 to 830 msec. Within this phase, the ectopic frequency was held at half the SN frequency. All points above the horizontal line represent slowing of the intrinsic frequency, and all points below the line represent acceleration. In the absence of modulation of EP, the two frequencies would be completely independent, and all points would fall on the horizontal line. A close fit was obtained when this graph was compared with a similar plot constructed from a computer program in which

the maximal electrotonic interactions were set at +20 and −20 percent with a reversal at 60 percent.

Fixed Coupling

In the computer model, a parasystolic focus protected by "entrance block" may fire with a fixed coupling interval over a relatively wide range of S-A nodal frequencies if the electrotonic influence of responses in the surrounding ventricle is great enough and if the intrinsic cycle length of the ectopic pacemaker is sufficiently close to an integral multiple of that of the dominant pacemaker.[3] Fixed coupling may also occur in clinical examples of parasystole,[5] and it can be demonstrated in the biologic model as well. When the spontaneous cycle of EP is scanned with electrotonic depolarizations of relatively large amplitude, the transition from maximal delay to maximal acceleration can be very abrupt (Fig. 3A). Under these circumstances, as the slope of the biphasic relation approaches unity, coupling intervals become nearly fixed at very short or very long values.

The critical dependence of the coupling interval of an ectopic beat on the phase relations between the normal and ectopic pacemaker cycles is illustrated in Figure 4, obtained from the sucrose gap model. In panels A and B, the upper traces represent intracell recordings from SN, driven at a cycle length of 1,000 msec. Transmembrane potentials from EP are traced in the lower records. The intrinsic cycle of the "ectopic pacemaker" (in the absence of electrotonic influence) was 1,550 msec, indicated by the action potentials traced with broken lines. In this experiment, the upstrokes of the action potentials recorded from EP were used to trigger the electronic switch across the gap (see Methods) to permit full action potential propagation from EP to SN and only electrotonic depolarizing influences in the opposite direction. In panel A the second (driven) SN response occurred at 58 percent of the EP intrinsic cycle (910 msec). The electrotonic influence of SN, apparent as a subthreshold depolarization in the EP transmembrane potential, increased the EP cycle length to 1,815 msec (17 percent delay). This response propagated across the gap and appeared in the SN record just a few msec in advance of the next driven response (F). In an electrocardiogram this would have been recorded as a "fusion" beat. In panel B the second SN occurred 920 msec after the first EP discharge, or at 59 percent of its intrinsic cycle. The electrotonic influence of SN then accelerated the EP discharge by 19 percent, to a cycle of 1,255 msec. The accelerated EP discharge in panel B also propagated across the gap and produced an interpolated and closely coupled premature beat (E) in the SN trace. Under these conditions, coupling intervals were either very brief, as in Figure 4B, or very long, as in Figure 4A. Intermediate intervals between the two extremes did not occur.

The critical timing of events in Figure 4, A and B, suggests that a slight acceleration of SN must lead to closely coupled "extrasystolic" activity, and a slight deceleration to complete absence of manifest ectopic activity. An example of this phenomenon was found in one of the computer programs in which the programmed electrotonic influence was ±15 percent and is illustrated in Figure 4C. The ordinate scale represents the cycle length in msec of successive ventricular responses; manifest premature responses with brief coupling intervals fall below the horizontal line that defines the simulated SN frequency. The ratio of intrinsic cycle lengths was almost the same as in the biologic examples illustrated in Figure 4, A and B. When the simulated SN frequency was 60 beats/min (cycle length 1,000 msec), the "ectopic pacemaker" (intrinsic cycle 1,575) generated responses that propagated to SN as closely coupled beats or as fusion beats, as in Figure 4, A and B. When the SN frequency was accelerated to 61 beats/min, a trigeminal rhythm appeared, with fixed coupling of the early premature responses. When SN was slowed to 59 beats/min, manifest ectopic activity disappeared, although 3:2 entrainment of EP was still present.

The sensitivity of the ectopic pattern to slight changes in the SN frequency is not unique to the cycle length ratios that characterize the experimental and computed examples in Figure 4. A similar set of patterns was recorded in the sucrose gap model when the intrinsic ratio of EP cycle to SN cycle was approximately 1.4. In the examples shown in Figure 5, re-

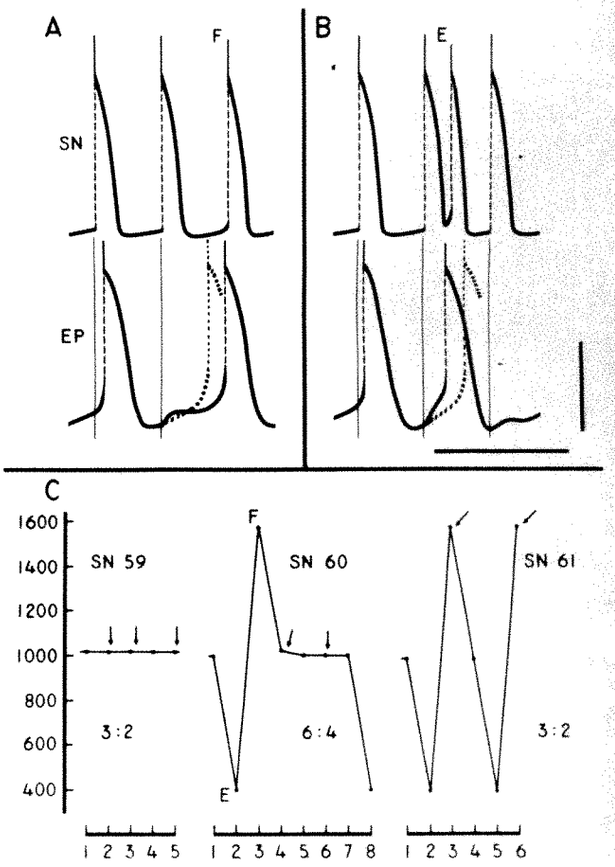


FIGURE 4. Fixed coupling related to phase relations between EP and SN. In **panels A** and **B, upper and lower tracing** are transmembrane potentials from SN and EP, respectively. SN cycle length = 1,000 msec; EP intrinsic cycle length = 1,550 msec (**broken line tracings**). In **panel A** the second SN response (**vertical line**) occurred at 910 msec of the EP cycle. In **panel B** the second SN response occurred at 920 msec. Transmembrane potentials were traced from a projection of the original recordings. Calibrations are 50 mv and 2,000 msec. **Panel C,** interval between successive responses; computer output translated into matching time. The **vertical scale** is in msec; the **horizontal axis** indicates the beat number. Numbers above the graphs indicate the simulated SN frequency. Numbers below the graphs represent the corresponding entrainment ratios. The **arrows** show the position of concealed ectopic discharges. Premature responses are followed by compensatory pauses. E = extrasystole; F = fusion beat.

corded in the same manner as those in Figure 4, A and B, the upper tracing in each panel is a simulated electrocardiogram, with the onset of the "R" waves coincident with the driven responses in the SN chamber; the lower tracings represent the spontaneous discharges of EP. The intrinsic cycle length of EP was 2,390 msec, indicated by the broken lines. In panel A of Figure 5 the SN cycle was set at 1,760 msec (intrinsic ratio 1.36). One-to-one entrainment of EP occurred; each response of EP occurred within the refractory period of SN, and there was no manifest ectopic activity. The operative ratio of EP to SN was thus reduced to 1.0. In Panel B a pattern similar to that in Figure 4 was recorded. When the driven cycle length of SN was abbreviated to 1,710 msec (a reduction of less than 3 percent), closely coupled "premature" interpolated responses alternated with fusion beats. In Panel C the driven cycle was further abbreviated to 1,670 msec, and a bigeminal rhythm resulted with fixed coupling of interpolated responses at an entrainment ratio of 1.0. The change from no manifest activity to bigeminy with fixed coupling occurred over a frequency range of only 5 percent.

Conduction Delay and Refractory Period

In the initial program of the mathematical model, propagation of a response from EP to SN was immediate and obligatory when SN was excitable; that is, no provision was made for delayed conduction within a relatively refractory period. Analysis of some clinical examples, together with the experiments reported in this study, demonstrate that this is an oversimplification and that conduction delay may also favor the phenomenon of fixed coupling.

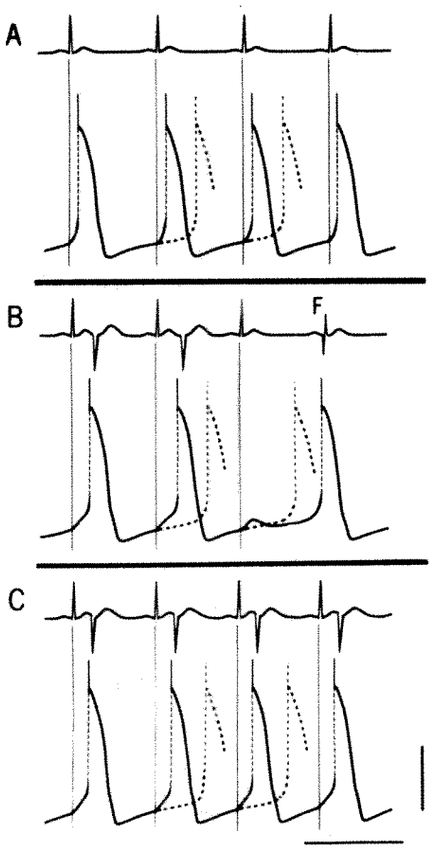


FIGURE 5. Coupling intervals and ectopic response patterns in relation to SN frequency. **Upper tracings** in each panel are simulated electrocardiograms constructed from projected transmembrane potential recordings in SN (chamber 3); **lower tracings** were recorded from EP. The intrinsic EP cycle length (2,390 msec) is indicated by the **broken line tracings.** SN cycle length was set at 1,760, 1,710 and 1,670 msec in **panels A, B** and **C,** respectively. Calibrations are 2,000 msec and 50 mv. F = fusion beat.

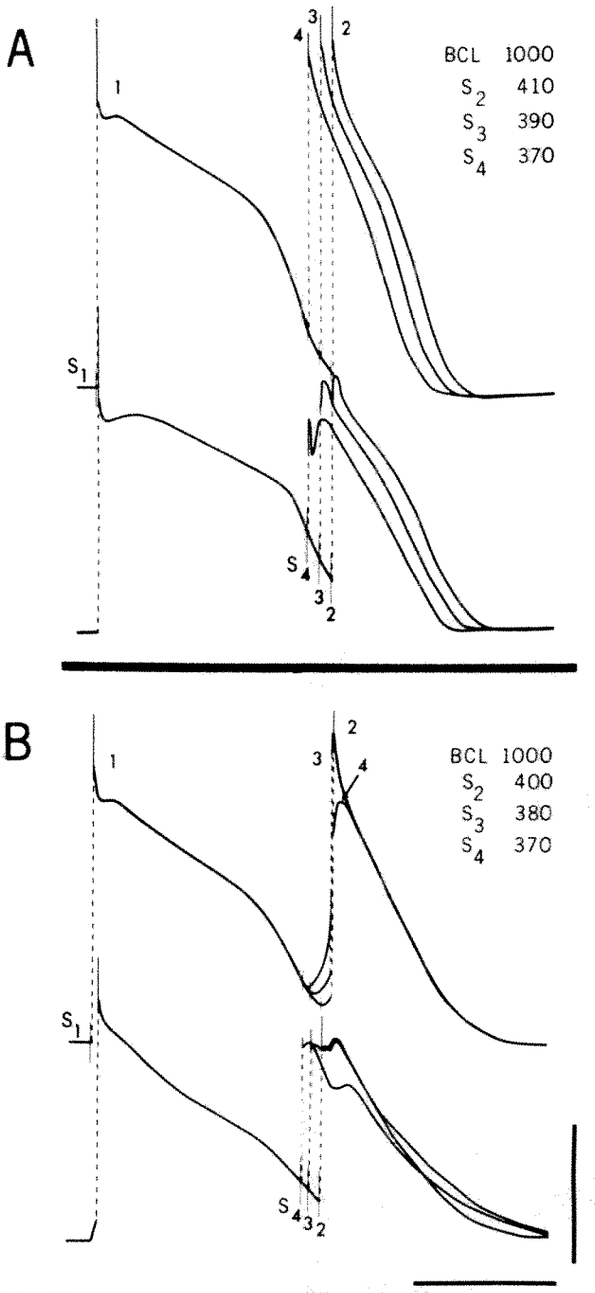


FIGURE 6. Dependence of the coupling interval on refractoriness and conduction delays. **Upper tracing in each panel** is a transmembrane potential recording from an SN cell (chamber 3); **lower tracing** represents transmembrane potentials from an EP cell (chamber 1). Basic stimuli (S_1) were applied to SN. Test stimuli (S_2, S_3 and S_4) were applied to EP at progressively briefer intervals. In **panel A,** all three chambers were perfused with normal Tyrode's solution. In **panel B,** 15 to 20 minutes of sucrose perfusion (shunt resistance 10 kilo-ohms) was used. Superimposed tracings are from projections of the original film. Calibrations are 250 msec and 50 mv. BCL = basic cycle length.

Figure 6 was obtained from a sucrose gap experiment in which the influence of refractoriness on conduction time and on coupling intervals was studied. In both panels, the upper tracings were recorded from SN and the lower tracings from EP. The same impalements were maintained in both panels. Panel A shows the results obtained when all three chambers were perfused with Tyrode's solution containing 4 mM potassium chloride. The superimposed traces show the responses to the last of 15 basic stimuli (S_1) applied to SN at a basic cycle length of 1,000 msec, and the responses to progressively earlier test stimuli (S_2, S_3 and S_4) applied to EP after every 15th basic response. Conduction time between the impaled cells when stimuli were applied at complete repolarization during diastole (not shown in the figure) was 4 msec. Although the amplitude of the EP action potentials decreased as the test stimulus interval was decreased, the conduction interval was not significantly affected; propagation occurred at nearly full speed, and the coupling intervals in SN were equal to the stimulus intervals.

The superimposed traces in panel B of Figure 6 were selected from the same experiment and were obtained 15 to 20 minutes after sucrose superfusion was started in the central chamber. The shunt resistance in the external pathway was set at a low value (10,000 ohms) to permit action potentials to propagate in both directions. Under these circumstances, the action potentials induced by the basic stimuli (S_1) were delayed by 10 msec between the impaled cells; this is apparent as a "foot" in the action potential of the EP response (Panel B, bottom tracing). When S_2 was applied to the EP end of the preparation at an interval of 400 msec, at a time when the fiber had not completely repolarized, the response crossed the gap and activated the SN cell with a conduction interval of 16 msec. When the test stimulus interval was decreased to 380 msec (S_3) and to 370 msec (S_4), conduction across the gap was delayed by 36 and 46 msec, respectively, and the "coupling interval" in SN was thus fixed at 416 msec, an interval equivalent to the functional refractory period of the system.

Clearly, the degree of refractoriness of the ventricles plays a role in determining the coupling intervals of premature beats originated in an ectopic pacemaker surrounded by an area of depressed excitability. When these provisions were incorporated into the computer programs, the model readily approximated the clinical examples.[3]

Bigeminy

In the initial study of electrotonic influences in the sucrose gap model, an attempt was made to induce a bigeminal rhythm. The stimulated end of the fiber was driven at a frequency twice the intrinsic frequency of the "ectopic" pacemaker, but bigeminy did not occur. After the computer model was developed,[3] it became apparent that (1) 2:1 entrainment occurs on both sides of the intrinsic ratio of 2 (Fig. 3), but manifest bigeminy can occur only at the upper extreme of that zone, that is, at intrinsic EP/SN ratios exceeding 2 by an amount that depends directly on the amplitude of the electrotonic influence; and (2) the range of ratios for manifest (and *stable*) bigeminy is surprisingly narrow. In addition, it was necessary to establish conditions for unidirectional ("entrance") block and for compensatory

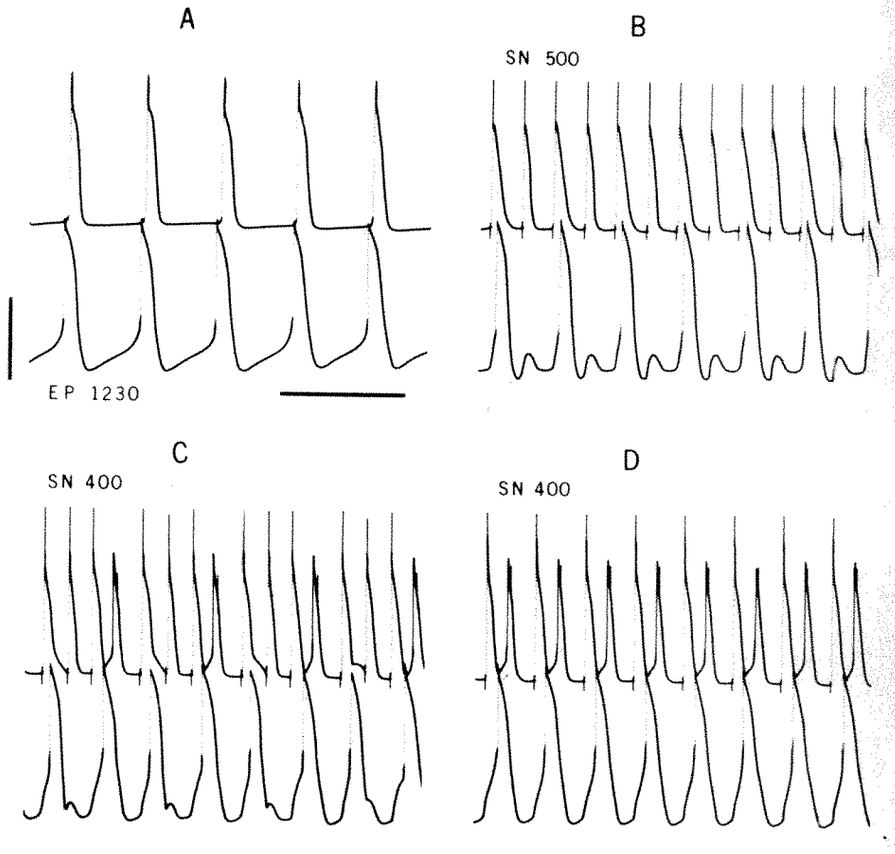


FIGURE 7. Bigeminy. **Panel A** shows the intrinsic EP cycle length (**lower tracing**). The shunt resistor permitted 1:1 propagation to SN (**upper tracing**). In **panel B,** SN was driven at a cycle length of 500 msec, and a 2:1 entrainment of EP was established, with all EP discharges falling within the refractory period of SN. In **panel C,** the SN cycle was set at 400 msec; 2:1 entrainment persisted but concealed bigeminy became apparent. In **panel D,** the value of the shunt resistance was slightly increased, producing a pattern of true bigeminy with each premature response followed by a compensatory pause. The impalements are the same in all panels. Transmembrane potentials were traced from projections of the original film. Calibrations are 2,000 msec and 50 mv.

pauses following the successful emergence of ectopic responses. When these mathematically obligatory conditions were met, it was possible to reproduce most of the computer-generated patterns in the biologic model.

Patterns of concealed and manifest bigeminy within a zone of 2:1 entrainment are illustrated in Figure 7. The upper tracings represent action potentials recorded from the SN end of the fiber, and the lower tracings represent those from the active pacemaker (EP). In panel A the pacemaker was allowed to beat spontaneously. These responses propagated to SN with a delay of about 100 msec. In panel B, SN was driven at a cycle length of 500 msec. Entrainment of EP occurred at a ratio of 2:1, that is, at an operative cycle length of 1,000 msec. EP fired within the refractory period of SN; accordingly, no manifest ectopic activity appeared. This is within one of the silent zones predicted by the mathematical model.[3] In panel C, the SN cycle was reduced to 400 msec; concealed bigeminy occurred at a 4:2 ratio, with every other EP response falling within the refractory period of SN. The manifest premature responses were followed by compensatory pauses, as the subsequent driving stimuli fell within the refractory period of the premature beat. As in the computer program, the actual EP cycles alternated between +50 and −50 msec from the average entrained cycle of 800 msec. In panel D, the amplitude of the electrotonic influence was decreased by adjusting the resistance in the shunt between the two chambers. Quadrigeminy was then replaced by manifest bigeminy in the SN end of the fiber.

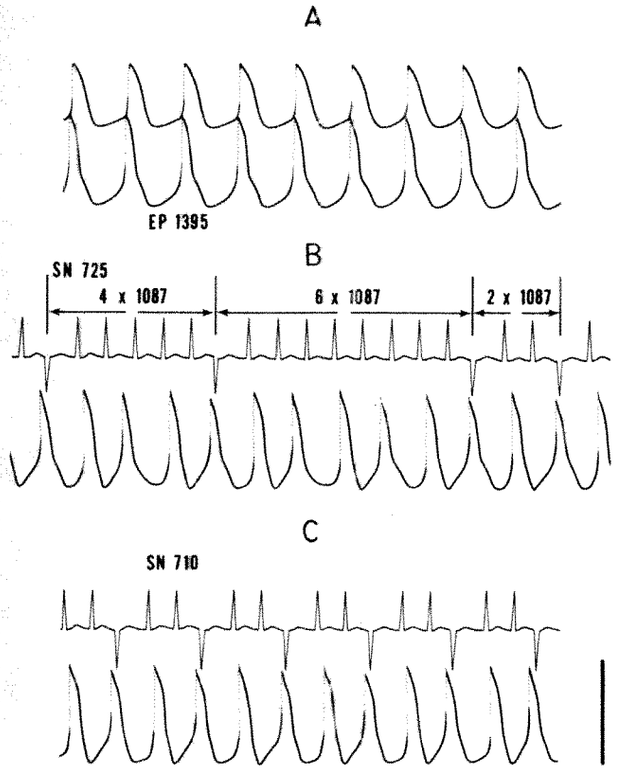


FIGURE 8. Trigeminy. The **upper tracing in each panel** corresponds to SN and the **lower tracing** to EP. **Panel A** shows the intrinsic EP cycle length with 1:1 propagation to SN. In **panel B,** SN was driven at a cycle length of 725 msec (intrinsic EP/SN ratio = 1.92). A 3:2 entrainment was present, and EP discharges propagated to SN with a pattern of concealed trigeminy (3n − 1). In **panel C,** the SN cycle length was decreased to 710 msec. Entrainment at 3:2 persisted, but trigeminy was apparent. The transmembrane potentials and simulated electrocardiogram in **panels B** and **C** were traced from projections of the original recordings. Calibrations are 3,000 msec and 100 mv.

The sequence of events in Figure 7 bears out the predictions of the mathematical model: acceleration of SN leads from silent entrainment to concealed bigeminy to frank bigeminy. Further acceleration, not shown in the figure, causes a break away from 2:1 entrainment.

Trigeminy

As predicted by the computer model, the entrained cycle length of EP is constant at the level of 2:1 entrainment. When the level is 3:2, cycles longer and shorter than average alternate, and ectopic activity can emerge in a pattern of concealed or frank trigeminy, depending on the intrinsic ratios.

The experiment illustrated in Figure 8 demonstrates this phenomenon. The top tracing in panel A shows transmembrane potentials recorded from SN; the bottom tracings in all panels were recorded from EP. The top tracing in panels B and C is a simulated electrocardiogram in which the upright "R" waves are traced at the moment of the recorded SN action potentials, and the downward dips represent the manifest "ectopic" responses propagated from EP. Panel A shows the control records during sucrose perfusion in chamber 2. The intrinsic cycle length of EP (bottom tracing, panel A) was 1,395 msec. The shunt resistor across the gap was adjusted to permit unidirectional action potential propagation from EP to SN; conduction time between the impaled cells was 68 msec. In panel B, SN was driven at a cycle length of 725 msec (intrinsic EP/SN ratio = 1,395/725 = 1.92). EP was entrained at 3:2; the average operative EP cycle was 1,087.5 msec, but the actual cycles alternated between 970 and 1,200 msec. Action potentials propagated from EP to SN with a constant coupling interval of 645 msec after every two, five or eight driven SN responses, producing the characteristic pattern of concealed trigeminy.[6] Note that the "interectopic intervals" fit the classic pattern of parasystole; all are simple multiples of 1,087, although none of the ectopic cycles fire at that interval. In panel C, the SN cycle length was decreased to 710 msec (intrinsic EP/SN ratio = 1.98). Entrainment persisted at the 3:2 operative ratio, and frank trigeminy appeared with a manifest premature response occurring after every two driven SN beats.

Figure 9 was constructed to permit a comparison between the events recorded in Figure 8B and the pattern that would have existed if there were no electrotonic interactions. Figure 9A is a diagram of the temporal relations between SN and EP, precisely as recorded in the episode of "concealed" trigeminy in Figure 8B. During this episode, the average cycle length of the ectopic pacemaker was reduced by nearly 25 percent as a result of the electrotonic influence of SN, that is, from 1,395 to 1,087 msec. If there had been no electrotonic influence, the pattern depicted in Figure 9B would have occurred. Starting at the same reference time as in Figure 9A, each of nine successive EP discharges would have fallen within the refractory period of SN, in a pattern that would reproduce itself approximately every 43 SN responses.

Quadrigeminy

A quadrigeminal pattern manifested in Figure 7C is an example of concealed bigeminy. "True" quadri-

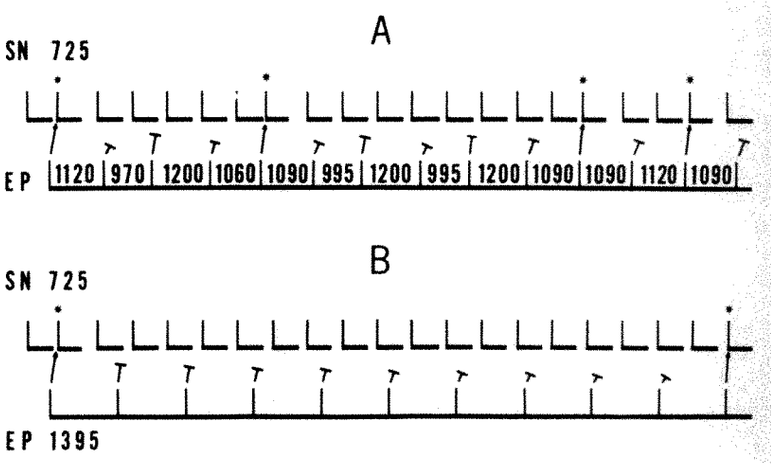


FIGURE 9. The diagram in **panel A** shows the temporal relations between SN and EP as recorded in Figure 8B and explains the mechanisms involved. **Panel B** represents the hypothetical case of a completely independent EP pacemaker firing at a fixed cycle length of 1,395 msec. The **vertical lines** indicate SN activation (driven cycle length 725 msec) in the **upper tracings** and time of EP discharge in the **lower tracings.** Refractory period in SN (560 msec) is indicated by the **horizontal lines.** Numbers between lines in **panel A** represent the electrotonically modulated EP cycle length. "Entrance" block from SN to EP was present in **panel A** (see Fig. 8) and was also assumed in **panel B.** The **oblique lines** indicate conduction from EP to SN. The varying inclination of these lines represents the varying conduction time through the sucrose gap, and the **short lines at right angles** to them indicate conduction block. Successful propagation from EP to SN is indicated by the **arrows** and the **asterisks.**

geminy is illustrated in Figure 10, taken from an experiment in which 2:1 entrainment was converted to 4:1 entrainment by a sudden change in the SN cycle length. In this experiment an electronic switch triggered by the upstroke of the EP action potential was used to shunt the two outer chambers (see Methods). The switch was maintained in the "on" position for 100 msec, permitting action potentials to propagate from EP to SN but only electrotonic depolarizations to pass in the opposite direction.

Figure 10A was recorded to illustrate the intrinsic cycle length of EP during sucrose perfusion of the central chamber, with the shunt pathway switched in. No stimuli were applied. In panel B, SN was driven at a cycle length of 1,000 msec. Action potentials did not propagate from SN (entrance block), but their electrotonic effects were manifest as a net acceleration of EP. The electrotonic modulation induced a 2:1 entrainment with every EP discharge falling within the refractory period of SN; no manifest EP activity appeared on the SN trace. Panel C was obtained 4 seconds after the basic driving cycle length of SN was suddenly reduced to 500 msec. A 4:1 entrainment was now present, with one EP propagating after every three SN beats and with a fixed coupling interval of 345 msec. Each propagated action potential was manifest as a premature beat in SN followed by a compensatory pause producing the typical pattern of a quadrigeminal rhythm.

Exit Block

The region of depressed conductivity that provides entrance block and "protection" of an ectopic focus may also be expected to impede the exit of impulses from the pacemaker. Intermittent first or second degree exit block has been invoked to explain perturbations of the rhythmic patterns in cases of parasystole. In some cases the patterns can be explained in terms of electrotonic modulation and entrainment of the parasystolic pacemaker,[3] but varying degrees of exit block surely must occur. An example published by Pick et al.[7] (their Figure 8) is reproduced in Figures 11 and 12. The cardinal feature in this case was ventricular tachycardia with alternation of the cycle lengths between 580 and 680 msec. In the construction of Figure 11A, Pick et al.[7] postulated an ectopic focus firing at a constant cycle length, with alternating conduction times in the exit pathway.

In Figure 11B action potentials are recorded from a spontaneously discharging pacemaker (lower tracing) in a sucrose gap preparation. One-to-one propagation across the gap was established by adjusting the shunt resistance to a level just short of that at which second degree block was manifest. Conduction time across the gap alternated between 30 and 90 msec and

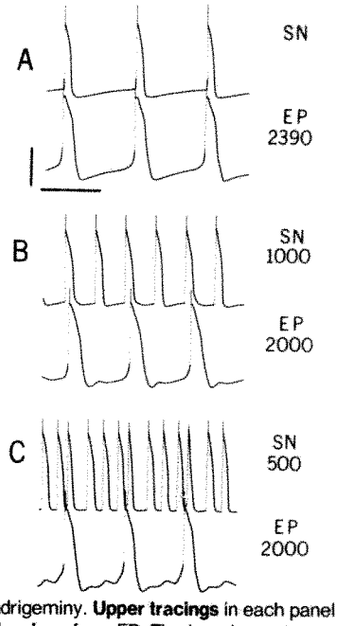


FIGURE 10. Quadrigeminy. **Upper tracings** in each panel are recordings from SN, **lower tracings** from EP. The impalements are the same in all panels. An electronic switch shunted the two outer chambers for 100 msec every time EP fired. **Panel A** shows the intrinsic EP cycle length. In **panel B,** SN was driven at a cycle length of 1,000 msec. EP was entrained at 2:1, and no premature discharges occurred. In **panel C,** a sudden change of the SN cycle length to 500 msec produced a 4:1 entrainment with one premature EP discharge (followed by a compensatory pause) propagating every third SN driven response. Tracings are drawn from projections of original film. Calibrations are 2,000 msec and 50 mv.

resulted in an alternation in the cycle lengths in the "ventricle" beyond the gap. The major difference from the postulated schema in Figure 11A is that the cycle lengths of the pacemaker itself also alternate, which is an obligatory consequence of the electrotonic influence of the action potentials generated beyond the gap. The delayed responses, indicated by the arrows, fell later in the ectopic pacemaker cycle and delayed the subsequent discharge slightly more than those that propagated more quickly. Nevertheless, the experimental results indicate that alternating conduction times can occur with one-to-one transmission.

In the example reproduced in Figure 12A, Pick et al.[7] postulated second degree block in the exit pathway, causing a 3:2 pattern between the ectopic focus (firing at a constant cycle length of 420 msec) and the surrounding ventricle. *In tracings recorded from another sucrose gap preparation (Fig. 12B),* the model exhibits a 3:2 Wenckebach pattern, leading to alternating cycle lengths in the tissue beyond the gap. Again, electrotonic effects reflected back to the pacemaker cause obligatory (and predictable) variations in the spontaneous cycle. Except for the postulated fixed rate of the pacemaker in the clinical case, the model demonstrates the feasibility of the proposed mechanism.

Discussion

Attributes and Criteria of Extrasystole

In the sucrose gap model of parasystole, we demonstrated that the patterns of ectopic activity and entrainment that result from electrotonic interactions across an area of depressed excitability depend on the magnitude of the electrotonic influence on the pacemaker cycle length and on the ratio of intrinsic frequencies, in a manner predicted by a mathematical model.[3] These results, together with previous reports from this laboratory, offer a plausible interpretation of parasystolic and other extrasystolic arrhythmias.

Unidirectional block: The concept of "entrance block," invoked by Kaufman and Rothberger[8] to explain the apparent independence of a parasystolic focus, is well established and is merely a special case of unidirectional block. The use of a sucrose gap in the biologic model is a convenient way of providing an area of depressed conductivity in imitation of the local conditions that must exist in the clinical situation.

It has been suggested that phase 4 depolarization may itself be responsible for the entrance block that protects a parasystolic focus.[9] The suggestion is based on the assumption that the reduced rate of depolarization (dv/dt of phase 0) that accompanies diastolic depolarization is the major determinant of conduction velocity. However, it is clear from previous observations that diastolic depolarization of a Purkinje fiber pacemaker facilitates rather than retards conduction.[2,10,11] As long as the threshold voltage at which phase 0 of the action potential is triggered remains constant, any approach to that threshold engendered by diastolic depolarization will improve the chance of capture of an ectopic pacemaker by an invading wave front from the surrounding tissue. Furthermore, the increased membrane resistance and the related increased space constant that are known to accompany slow diastolic depolarization increase the magnitude of the electrotonic depolarization that precedes the advancing wave front (Fig. 2A).

The conditions that favor one-way block (local ischemia, local elevation of potassium, asymmetric stretch) are all likely to occur in damaged myocardium. Like the sucrose gap, the region of impaired conductivity does not need to "conduct" an impulse; it only needs to serve as an ionic channel for the transmission of electrotonic

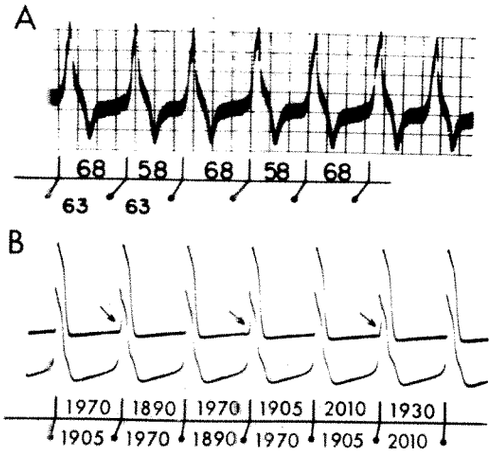


FIGURE 11. Example of "exit block" from a parasystolic focus published by Pick et al.[7] as their Figure 8 (reproduced from Fisch, C: Complex Electrocardiography I, Cardiovascular Clinics, Vol 5, no. 3; Philadelphia, FA Davis, 1973, with permission of the authors and publishers). **Panel A** shows a lead III electrocardiogram from a patient with ventricular tachycardia with alternating cycle lengths. The **diagram below the tracing** shows a hypothetical ectopic pacemaker discharging at a fixed rate and propagating with alternating brief and long conduction delays. **Panel B** was recorded from a sucrose gap preparation. The **upper tracing** corresponds to SN, the **lower tracing** to EP. The **diagram under panel B** indicates the actual cycle durations and conduction delays across the gap. Note that when EP propagates promptly, SN occurs very early and the EP cycle is brief. When EP propagates slowly (**arrows**), SN occurs late and the EP cycle is prolonged.

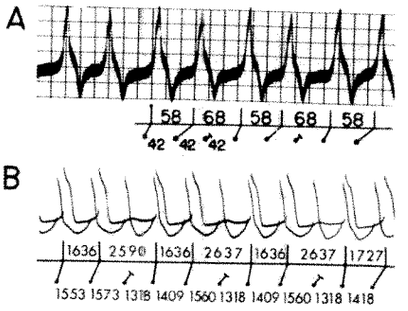


FIGURE 12. Same example as in Figure 10 (reproduced from Pick et al.,[7] with permission), showing a second possible mechanism for ventricular bigeminy (**panel A**). Panel B was obtained from a sucrose gap preparation and shows an equivalent experimental record. A 3:2 Wenckebach periodicity between EP (**lower tracing**) and SN (**upper tracing**) is apparent. EP did not fire at a fixed rate, but its cycle length varied according to phase relations.

influences. The degree of block, which will determine the amplitude of the electrotonic influence, will depend on the length of the depressed area, the geometry of the system and on the passive and active electrical properties of the tissues involved.

Fixed cycle length: The fixed cycle length believed to be a necessary attribute of classic parasystole is clearly not a proper diagnostic criterion. This was apparent in the analysis of the mathematical model[3] and also in the biologic model. In the example illustrated in Figure 2C, interectopic intervals encompassing two and one ectopic cycles are related as 1.67 to 1, not 2 to 1. In a comparable clinical record one could postulate that the actual frequency of the ectopic pacemaker was three times as fast as EP in that illustration, yielding the desired simple harmonic ratio of 5:3; however, that supposition would necessitate the further supposition that intermittent exit block conceals the true situation. Electrotonic interaction explains the situation in terms of pacemaker modulation. Fixed cycle length cannot be an obligatory feature of a parasystolic focus.

There are occasions when the classic common denominator hypothesis applies to manifest interectopic intervals in the experimental model and, presumably, also to clinical situations. A fortuitous example is evident in Figure 8B, in which all of the interectopic intervals are simple multiples of 1,087 msec, although the actual ectopic cycles vary between about 970 and 1,205 msec.

Entrainment of the pacemaker: Entrainment of an ectopic pacemaker is an obligatory consequence of its electrotonic interaction with the surrounding tissue. Wide zones of entrainment at simple ratios (1:1, 2:1, 3:1) are the rule in both the mathematical and biologic models. The breadth and position of the entrainment zones is a function of the amplitude of the interaction and also of the symmetry of the positive and negative phases and of the point in the pacemaker cycle at which the switch from positive to negative occurs. In the example shown in Figure 3, the zone of 2:1 entrainment extends from an intrinsic ratio of about 1.7 to nearly 2.5, when the measured electrotonic modulation of the pacemaker cycle was +21 and −26 percent at the respective maxima. When the biphasic curve of influence recorded in another experiment, in which the measured modulation reached 30 percent, was translated to the computer model, the 2:1 zone extended from an intrinsic ratio of 1.8 to nearly 3.0. The consequence of interaction of that magnitude is illustrated in Figure 7, in which manifest bigeminy was present when the intrinsic ratio of cycle lengths was 1,230/400, or greater than 3 to 1.

Fixed coupling: Fixed coupling of premature responses could occur by chance even if the ectopic pacemaker were completely independent of electrotonic influence from the surrounding tissue. Where entrainment of the pacemaker occurs, as was shown in the mathematical model, fixed coupling can be obligatory over certain broad frequency ranges. Fixed coupling was an even more striking attribute of the biologic model, as demonstrated in the experiments shown in Figures 4 and 5. The sharply defined phase shift from maximal delay to maximal acceleration in those experiments was responsible. A natural consequence is that shifts between frequent and closely coupled premature depolarizations (as in "extrasystolic" bigeminy) and complete silence may accompany minor changes in the frequency of the dominant pacemaker (Fig. 4C and 5). If the efficacy of an antiarrhythmic drug is to be assessed in terms of reduced incidence of ectopic activity, it is important to determine how much of the effect may be a simple consequence of a change in the basic heart rate.[12,13] Atropine, for example, could be a remarkably effective antiarrhythmic agent under certain conditions, not by "overdrive suppression" of an ectopic pacemaker, but by accelerating the heart to a range where the EP/SN ratio falls in a "silent" zone.

Conduction delays: first and second degree exit block: In the mathematical model, conduction delay was, for convenience, not incorporated in most of the computer runs.[3] It is perhaps surprising that so many features of clinical arrhythmias appeared to fit the model because conduction delays of varying degrees must surely occur in living tissue. Even examples previously attributed specifically to second degree exit block could be matched almost quantitatively by the model. If, as in the mathematical model, the ventricular response to an ectopic discharge and the ectopic event itself are programmed to occur simultaneously, the resulting ventricular event can have no reciprocal influence on the ectopic pacemaker. But both entrance and exit delays are clearly evident in the biologic model. When the exit delay is minimal, the manifest ectopic response in the ventricle occurs too early to cause an appreciable prolongation of the pacemaker cycle. If the exit delay is large (it can exceed 100 msec even in the sucrose gap model) and if the intrinsic cycle is brief, then a significant reciprocal influence may be expected. This is clearly quantitatively significant in estimating the magnitude of pacemaker interactions but probably does not greatly alter the basic analysis of parasystolic pacemaker behavior. For example, the experiments illustrated in Figures 11 and 12 demonstrate that first and second degree exit blocks can and do occur in the biologic model but that the variations in conduction intervals result also in predictable variations in the ectopic cycle lengths. The difference between the experimental models and the hypotheses invoked to explain the clinical pattern is thus only a quantitative detail.

Patterns of ectopic activity in the biologic model: One of the lessons learned from the mathematical model was that stable patterns of bigeminy and trigeminy did not occur at the expected intrinsic ratios of 2:1 and 3:1 but were displaced to the right in the respective entrainment zones. When the electrotonic influence was great, the displacement was unexpectedly large. When these lessons were applied to the sucrose gap model, bigeminy and trigeminy were readily demonstrable.

Zones of concealed bigeminy and trigeminy were also demonstrable in the biologic model. As predicted, they fell within the 2:1 and 3:1 entrainment zones immediately to the left of the zones of bigeminy and trigeminy. Other patterns, including wide zones of "silence," were

also demonstrable in the sucrose gap model, lending support to the general hypothesis that many patterns of ventricular ectopic activity previously ascribed to other mechanisms may be the result of the modulated discharge of parasystolic foci.

Diagnostic Implications

The possible clinical implications of these observations are largely negative. A constant cycle length of a protected ectopic pacemaker, evident by interectopic intervals that are simple multiples of a common denominator, is *not* a requirement for the diagnosis of parasystole. Fixed coupling of ectopic responses to the preceding normal event is *not* incompatible with parasystole; over rather broad ranges of heart rate, it may even be an obligatory feature of parasystole.

Ventricular parasystole is considered uncommon and benign. Both of these attributes are the consequence of a much too restrictive application of the accepted diagnostic criteria. A parasystolic focus *is* capable of generating closely coupled responses. There is always the likelihood of serious or fatal disorganization of the ventricular rhythm when an abnormal impulse is discharged during the "vulnerable" period of the heart, whether the impulse is generated by a pacemaker or by a reentrant circuit; it is even possible for the ectopic discharge to initiate a reentrant circuit. The only dangerous premature beat is the one that results in sudden death.

The model reported here is a biologic confirmation of the mathematical model described earlier, and the results emphasize the importance of the ratio of the intrinsic cycle lengths of the ectopic pacemaker (EP) and the sinus nodal pacemaker (SN) in determining the patterns of manifest ectopic activity. As the ratio is changed, whether by altering the basic heart rate or by changing the rate of the ectopic focus, predictable pattern changes must occur.[3] Pattern changes must also accompany acceleration of the heart if the mechanism is reentry, but the relation of the patterns to the frequency is likely to be different. The pattern changes that accompany gradual alteration of the heart rate, induced by intracardiac stimulation or by graded doses of atropine, can provide the diagnostic clues.

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Mechanism of Reduction of Mitral Regurgitation With Vasodilator Therapy

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Acute mitral regurgitation was produced in six open chest dogs by excising a portion of the anterior valve leaflet. Electromagnetic flow probes were placed in the left atrium around the mitral anulus and in the ascending aorta to determine phasic left ventricular filling volume, regurgitant volume and stroke volume. The systolic pressure gradient was calculated from simultaneously measured high fidelity left atrial and left ventricular pressures. The effective mitral regurgitant orifice area was calculated from Gorlin's hydraulic equation. Infusion of nitroprusside resulted in a significant reduction in mitral regurgitation. No significant change occurred in the systolic pressure gradient between the left ventricle and the left atrium because both peak left ventricular pressure and left atrial pressure were reduced. The reduction of mitral regurgitation was largely due to reduction in the size of the mitral regurgitant orifice. Reduction of ventricular volume rather than the traditional concept of reduction of impedance to left ventricular ejection may explain the effects of vasodilators in reducing mitral regurgitation.

The factors that determine the regurgitant flow in mitral insufficiency are the size of the regurgitant valve orifice or the area of the deficit in mitral closure, the duration of the regurgitation or the length of ventricular systole and the systolic pressure gradient between the left ventricle and the left atrium.[1,2] Traditionally, it has been accepted that the regurgitant orifice size is fixed under different circulatory states[1] except in the clinical syndrome of papillary muscle dysfunction in which the properties of the supporting structures may change with time.[3–5] However, Borgenhagen et al.[6] suggested that the size of the regurgitant orifice is not fixed. Recently, we[7] found that volume expansion and pressure loading increased mitral regurgitation by increasing the regurgitant orifice size, whereas augmentation of myocardial contractility decreased the regurgitation by reducing the size of the regurgitant orifice. Thus, in experimental acute mitral insufficiency, altering the size of the regurgitant orifice plays a major role in the magnitude of regurgitation.

It is generally thought that the hemodynamic effect of reducing the regurgitation in mitral insufficiency with vasodilator therapy is due to the reduction of left ventricular impedance by decreasing the systemic vascular resistance.[8–11] However, the magnitude of mitral regurgitation is related directly to the product of the regurgitant orifice size and the square root of the systolic pressure gradient between the left ventricle and the left atrium. Thus, factors altering the regurgitant orifice size will affect the regurgitation relatively more than similar changes in the systolic pressure gradient. This study was designed to define more precisely the basis of the beneficial hemodynamic effects of nitroprusside in experimental acute mitral regurgitation.

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Methods

Animal preparation: Six mongrel dogs, weighing 20 to 30 kg, were anesthetized with sodium pentobarbital (25 mg/kg body weight intravenously) and artificially ventilated. The animal preparation was described previously.[12] Briefly, after a mid line sternotomy and bilateral thoracotomy in the fifth intercostal space, the pericardium was opened and the heart was supported in the pericardial cradle. Left ventricular and left atrial pressures were measured with high fidelity microtip catheters (Millar) that were introduced into the left ventricle and the left atrium through the apical dimple and the pulmonary vein, respectively. Aortic pressure was measured with a Statham P23Db transducer connected to a short (30 cm) catheter introduced into the right carotid artery. All three transducers were adjusted to equal sensitivity and a common 0 level. The first derivative of left ventricular pressure (dP/dt) was obtained with a resistance-capacitance differentiator. An electromagnetic flow transducer (Carolina Medical Electronics) was placed around the ascending aorta.

While the animal was on complete cardiopulmonary bypass, the left atrium was opened and an electromagnetic flow probe with a Dacron® sleeve was sutured around the mitral anulus. Special care was taken to suture the sleeve of the probe to the anulus, so that it did not interfere with mitral ring mobility and the freedom of cusp movement. Thus, the mitral valve apparatus remained intact. Phasic mitral and aortic flows were measured with a two channel square wave flowmeter (Carolina Medical Electronics). Under direct vision, acute mitral regurgitation was produced by excising a portion of the free edge of the anterior leaflet. The left atrium was then closed. Normal sinus rhythm was restored with direct current defibrillation, and the animal was weaned from circulatory bypass.

Calculation of cardiac volumes: Filling volume, regurgitant volume and forward stroke volume were calculated by digitizing the flow curves with a sonic digitizer (Science Accessories) coupled to a programmable calculator (Hewlett-Packard 9820). The average of 3 to 5 determinations was used for each calculation. Zero mitral flow probe was determined initially while ventricular fibrillation was still present, during the experiment by producing long postextrasystolic diastolic periods, and again at the end of each experiment by arresting the heart with potassium chloride. The regurgitant volume is the negative area of the mitral flow curve and the filling volume, which equals the total stroke volume, is the positive area of the mitral flow curve (Fig. 1). In a steady state, stroke volume plus regurgitant volume equals the total left ventricular stroke volume. The mean systolic pressure gradient between the left ventricle and the left atrium was determined from simultaneous left ventricular and left atrial pressure curves and was calculated using the same digitizing system (Sciences Accessories).

Regurgitant orifice calculation: The mean area of the regurgitant orifice (MRA) during ventricular systole was calculated from Gorlin's hydraulic equation: $MRA = (RV/RT)/K\sqrt{SPG}$, where RV = regurgitant volume (ml), RT = regurgitant time (sec) measured directly from the mitral flow curve and SPG = systolic pressure gradient (Fig. 1). K is the constant, which has a value of 37.9 as recently revised by Cohen and Gorlin[13] and confirmed in a more recent study.[14] The forward cardiac output was calculated from the product of heart rate and stroke volume. We demonstrated that in a fixed regurgitant orifice, using a tilting-disc mitral valve prosthesis with a 5 mm diameter hole, the Gorlin formula is valid.[15]

Nitroprusside infusion: Thirty to 45 minutes after completion of the surgical preparation, the animal's condition was stable and hemodynamic data were collected for analysis. Nitroprusside was administered by continuous intravenous infusion (average dose 100 μg/min) to lower the systolic blood pressure by 10 to 20 mm Hg. All pressures and flow curves were recorded on an oscillographic recorder (Electronics for Medicine DR 12) at a paper speed of 100 mm/sec. The standard Student's *t* test was used for statistical analysis (paired data).

Results

Hemodynamic effects of nitroprusside: Representative original records illustrating the hemodynamic effects of nitroprusside are shown in Figure 1. They

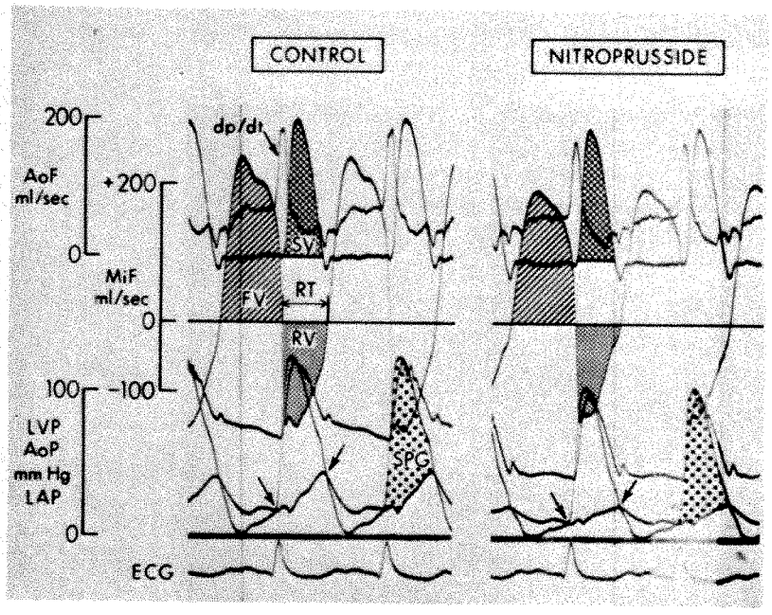


FIGURE 1. Effects of nitroprusside infusion: Original tracing obtained during control period (**left panel**) and during nitroprusside infusion (**right panel**). AoF = aortic blood flow; AoP = aortic pressure; dp/dt = first derivative of left ventricular pressure; ECG = electrocardiogram; FV = filling volume; LAP = left atrial pressure; LVP = left ventricular pressure; miF = mitral blood flow; RT = regurgitant time; RV = regurgitant volume; SPG = systolic pressure gradient; SV = forward left ventricular stroke volume. The two **arrows** in the **lower panels** indicate the left ventricular and left atrial pressure crossover points. Note the decrease in both peak systolic pressure and left atrial pressure; thus the systolic pressure gradient remained essentially the same.

TABLE I

Hemodynamic Effects of Nitroprusside

	LVSP	LVEDP	LA *V*	CO	SV	SV/RV	SVR	dP/dt
C	120.3 ± 6.9	14.7 ± 1.0	41.4 ± 2.0	2.46 ± 0.22	14.6 ± 1.5	1.45 ± 0.32	2767 ± 72	2890 ± 230
NP	109.0 ± 7.1	10.3 ± 1.2	26.3 ± 2.1	2.42 ± 0.20	13.7 ± 1.4	1.83 ± 0.36	2331 ± 85	2690 ± 280
P	<0.02	<0.001	<0.001	NS	NS	<0.001	<0.005	NS

C = control; CO = cardiac output (liters/min); dP/dt = first derivative of left ventricular pressure (mm Hg/sec); LA *V* = left atrial *V* wave (mm Hg); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVSP = left ventricular systolic pressure (mm Hg); NP = nitroprusside; NS = not significant; *P* = probability; RV = regurgitant volume; SV = forward left ventricular stroke volume (ml); SVR = systemic vascular resistance (dynes sec cm^{-5}).

demonstrate substantial reductions in regurgitant volume, filling volume, left ventricular end-diastolic pressure and left atrial *V* wave. The forward left ventricular stroke volume remained unchanged. The reduction in both peak left ventricular systolic pressure and left atrial pressure resulted in a small decrease in the ventricular-left atrial systolic pressure gradient.

During the administration of nitroprusside, systemic blood pressure and left ventricular end-diastolic pressure decreased, respectively, from 120.3 ± 6.9 to 109 ± 7.1 mm Hg (P <0.02) and from 14.7 ± 1.0 to 10.3 ± 1.2 (P <0.001) (Table I). Forward cardiac output, stroke volume and left ventricular dP/dt were essentially unchanged. The ratio of forward stroke volume to regurgitant volume increased by 26 percent, from 1.45 ± 0.32 to 1.83 ± 0.36 (P <0.001). The left atrial *V* wave decreased from 41.4 ± 2.0 to 26.3 ± 2.1 mm Hg (P <0.001), and systemic vascular resistance was reduced from 2,767 ± 72 to 2,331 ± 85 dynes sec cm^{-5} (P <0.005).

Regurgitant volume and mitral regurgitant orifice: In seven observations obtained during nitroprusside infusion, there was a 26 percent reduction in regurgitant volume, from 12.2 ± 2.1 to 9.0 ± 1.7 ml (P <0.01, Fig. 2A). The regurgitant fraction of the total left ventricular stroke volume decreased by 17 percent, from 43.7 ± 4.2 to 36.4 ± 3.7 percent (P <0.001, Fig. 2B). Because both peak left ventricular pressure and left atrial pressure decreased, the sytolic pressure gradient between the left ventricle and the left atrium remained unchanged (Fig. 2C). The calculated area of the mitral regurgitant orifice decreased by 18 percent, from 0.265 ± 0.043 to 0.217 ± 0.038 cm^2 (P <0.01, Fig. 2D). If the mitral regurgitant orifice area had remained unchanged, the calculated regurgitant volume (derived from Gorlin's hydraulic formula) associated with the decreased systolic pressure gradient (from 62.1 ± 6.6 to 58.3 ± 6.4 mm Hg) would have decreased from 12.2 to 11 ml. In fact, the measured regurgitant volume was reduced to 9 ml. This is due to the significant reduction in the size of the effective regurgitant orifice from 0.265 ± 0.043 to 0.217 ± 0.038 cm^2 (P <0.01, Fig. 2D).

Discussion

Previous studies of the dynamics of mitral regurgitation either have not measured regurgitant volume[16] or have eliminated the role of the entire mitral apparatus.[17,18] In this study, the direct measurement of phasic transmitral flow by an electromagnetic flow probe placed around the mitral anulus, together with the measurement of aortic flow, enabled us to calculate, on a beat to beat basis, filling volume, stroke volume and regurgitant volume. When these data were combined with measurements of ventricular and atrial pressure, we were able to calculate the size of the regurgitant orifice area.

Factors affecting mitral regurgitant volume: The regurgitant flow across the incompetent mitral valve is related to the systolic pressure gradient, the size of the regurgitant orifice and the duration of ventricular systole.[1,2] If, as is widely accepted, the regurgitant orifice area is fixed, except in the clinical syndrome of papillary muscle dysfunction,[3–5] the regurgitant volume should be a function only of the systolic pressure gradient.

In a recent investigation[7] of the effects of ventricular volume, pressure and contractility on the effective

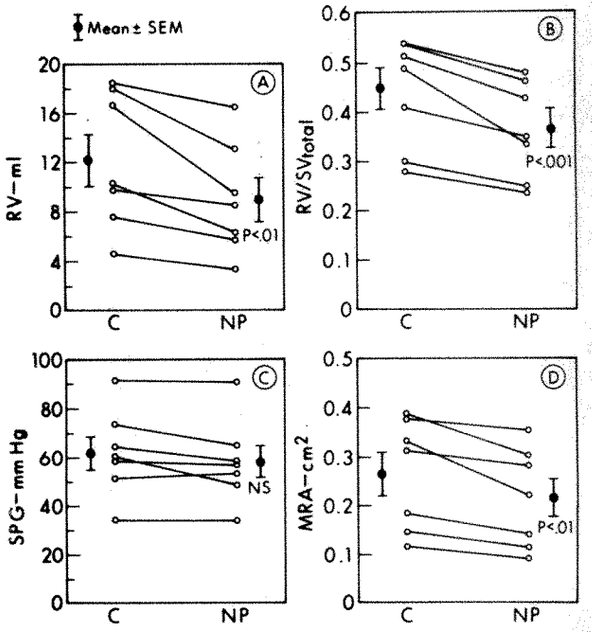


FIGURE 2. The effects of nitroprusside (NP) infusion on control (C) values. The **solid circles** and the **vertical bars** indicate mean values and standard error of the mean (SEM), respectively. **A,** RV = regurgitant volume. **B,** RV/SV total = calculated ratio of regurgitant volume to total left ventricular stroke volume. **C,** SPG = mean systolic pressure gradient between the left ventricle and left atrium. **D,** MRA = calculated area of the mitral regurgitant orifice. NS = not significant; P = probability.

regurgitant orifice area, we found that augmentation of ventricular afterload by angiotensin and increase of preload by volume infusion tended to enlarge the ventricle, to widen the anulus and to increase the effective regurgitant orifice area. Conversely, augmentation of myocardial contractility decreased the effective regurgitant orifice area, presumably by decreasing ventricular volume, despite an increase in the systolic pressure gradient.[7] Our work thus supports the findings of Borgenhagen et al.[6]

Mechanism of reduction of mitral regurgitation by nitroprusside: Normal function of the mitral valve apparatus depends on the mechanical integrity of the mitral anulus, the valve leaflets, the chordae tendineae and papillary muscles as well as on the contraction of the free wall of the left ventricle. Moreover, because the size of the anulus varies during systole,[19] it can actively participate in controlling the orifice size of the mitral valve. The regurgitant orifice may therefore change under different hemodynamic conditions.

The reduction of mitral regurgitation induced by nitroprusside demonstrated in our study is in agreement with the results of other investigators.[8–11] However, we did not find a significant increase in forward cardiac output or stroke volume. Left ventricular end-diastolic pressure was not excessively high (14.7 ± 1.0 mm Hg), and administration of nitroprusside caused a reduction in ventricular filling pressure to 10.3 ± 1.2 mm Hg. Thus, the reduction in the forward cardiac output in our study can be explained by the Frank-Starling mechanism because these hearts were operating on the steep portion of the stroke volume-filling pressure curve.

The reduction of mitral regurgitation by nitroprusside is currently considered to be due to the decrease in systemic vascular resistance or to the decreased impedence to left ventricular ejection.[8–11] Little attention has been given to other factors that may independently influence mitral regurgitation. Chatterjee and Parmley and their co-workers[8,11] did speculate that an additional effect of nitroprusside may be to enhance the competence of the mitral valve by improving the function of the subvalve apparatus secondary to decreased left ventricular chamber size, as shown by Borgenhagen et al.[6]

In our study, the administration of nitroprusside caused a reduction of both peak systolic pressure and left atrial pressure. Thus, the systolic pressure gradient was only slightly reduced. This small (insignificant) reduction of the systolic pressure gradient cannot explain the significant reduction in regurgitant volume. On the basis of control orifice size, 38 percent of the decrease in regurgitant volume after nitroprusside can be explained by the decrease in systolic pressure gradient, whereas 62 percent is due to a reduction in the effective regurgitant orifice area. Nitroprusside resulted in significant decreases in left atrial pressure and left ventricular filling pressure, suggesting a reduction in ventricular volume. Thus, the mechanism of the decrease in the effective regurgitant orifice appears secondary to its major venodilator action on the capacitance bed and reduction of the ventricular volume.

Greenberg et al.[20] recently demonstrated that hydralazine reduced regurgitation by improving forward flow without affecting ventricular volume or ejection fraction. Their findings differ from ours and may be due to the dual vasodilating effects of nitroprusside (arteriolar and venous) in contrast to the arteriolar effects of hydralazine.

Clinical implications: The relation of this experimental model of acute mitral insufficiency to clinical conditions is only speculative. In this preparation, the mitral apparatus remained intact except for partial excision of the anterior leaflet, whereas in clinical mitral regurgitation other structures may be involved. However, this model may represent the problem of acute mitral regurgitation due to ruptured chordae tendineae.

Our findings indicate that in experimental acute mitral insufficiency the regurgitant orifice is not a fixed structure. Nitroprusside reduces regurgitation primarily by decreasing the regurgitant orifice size as a result of the reduction in ventricular volume. In principle, reduction of afterload is beneficial to forward cardiac output, but its direct effect on regurgitant volume has not been definitively established.

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Detection of Coronary Artery Disease With Rapid Serial Rescanning With Potassium-43 at Rest

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To improve the sensitivity and accuracy of the detection of coronary artery disease with potassium-43 imaging at rest, a rapid serial scanning technique was developed to detect appearance time and sequence of myocardial isotope accumulation. The group of 85 patients included normal subjects and patients with angina pectoris, myocardial infarction and miscellaneous nonischemic heart diseases. Each patient also underwent coronary angiography and left ventriculography and the results were compared with the results of scanning. An angiographically demonstrable obstruction of 50 percent or greater luminal diameter in a coronary artery was found in 95 percent of the patients whose first serial myocardial scan at rest, accomplished 4.5 minutes after isotope administration, showed delayed regional appearance or abnormal sequence of accumulation of radioactivity by the end of the second scan. Eighty-five percent of individual lesions in a major coronary artery identified by scanning were found at the same site on angiography. Ventricular aneurysms were demonstrated as positive images during the first serial scan, although later scans showed no myocardial activity. Collateral circulation was demonstrable on serial scanning and, when angiographic evidence of such circulation was available, the recipient arterial bed was always correctly identified. In 32 patients who underwent myocardial imaging at rest and after graded exercise testing, the images at rest correlated better with the angiographic data. In conclusion, rapid serial scanning at rest detected coronary arterial lesions of 50 percent or greater, collateral circulation and, often, ventricular aneurysms as positive images.

When radioactive potassium or one of its analogs is used, single myocardial perfusion scans of 10 minutes or longer are not always indicative of abnormal myocardial perfusion patterns in patients with coronary artery disease. This is especially true when the degree of arterial stenosis is less than 90 percent or when collateral arterial anastomoses are present. To assess the functional reserve of the coronary circulation, Zaret et al.[1,2] used treadmill exercise to maximal physical tolerance or to the point of angina pectoris as a means of inducing or amplifying abnormal myocardial perfusion patterns. However, there is no unanimous agreement whether such stressing is capable of eliciting the true coronary reserve present in patients so tested.

This study had two objectives: (1) to develop a rapid serial rescanning technique capable of detecting appearance time and sequence of accumulation of the isotope in the myocardium, and (2) to evaluate the accuracy of this technique.

Material and Methods

Patients: A group of 85 patients who were suspected of having coronary artery disease or who had previously had a myocardial infarction or revascularization surgery underwent myocardial perfusion scanning with potassium-43. Of this group, 32 underwent scanning both at rest and after graded treadmill exercise.

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Coronary angiography and left ventriculograms were performed in all patients within 6 weeks (usually less than 2 weeks) after the scanning procedure.

Isotope dose and administration: The maximal dose of potassium-43 per study was 1 millicurie. The potassium-43 was diluted in 10 ml of saline solution and given as a bolus injection in an antecubital vein. The total whole body absorbed radiation from such a dose has been computed to be 430 to 500 millirads, depending on the method of calculation.[3,4]

Resting scans: In the early studies, the bolus dose of radioisotope was given intravenously with the patient erect. Positioning the patient in the supine position on the rectilinear scanner caused almost a 5 minute delay between injection and scanning. Because this delay proved too long to demonstrate early isotope appearance time, nearly all of the later studies were accomplished with the patient supine on the scanning table so that the potassium-43 could be administered while the detector was scanning extracardiac structures. This procedure allowed completion of the first scan within 4 to 4.5 minutes after injection of the radioisotope; the total time required for such a scan was 5.5 minutes. Another series of 5.5 minute scans was always obtained without pause except to change the patient to the left anterior oblique position after completing four scans in the anteroposterior aspect.

Exercise scans: In an attempt to detect coronary lesions that limited flow only under conditions of increased demand, 32 patients performed a graded treadmill exercise test under electrocardiographic monitoring. The potassium-43 was administered at the point of angina pectoris or fatigue or when the target heart rate had been reached without symptoms. After the recovery period (that is, when heart rate had returned to the control value) the patient was transported to the scanning laboratory where myocardial imaging was accomplished as described for the scans performed at rest. Patient recovery and transport caused an 8 to 10 minute delay between administration of the radionuclide and start of the first scan.

Scanning technique: A digital rectilinear dual detector radionuclide scanner was designed and constructed for detection of high energy gamma radiation (up to 1.5 mev).[5] This extensive shielding produces a lower background level with less energetic gamma rays such as those from potassium-43. Collimation was designed for a 662 kev (cesium-137) gamma range allowing dual channel pulse-height analysis to be used to sum the counts from the dual paired (370–390 and 590–620 kev) peaks of potassium-43.[6] High speed scanning is a standard capability with the dual binary counters and fast (150 characters/sec) perforated paper tape recording system. To simulate a single scan of longer duration, four serial scans were summed element by corresponding element using computer techniques. Because these summed images had a count density of approximately 1,000/cm^2 in the region of interest, 9 point averaging of the individual serial scans was done after the summation process. Averaging these was necessary because of the reduction in detected counts caused by fast serial scanning. Display of the images was accomplished by a cathode-ray tube with dot position and intensity (32 levels) under computer control. Permanent records were made on Polaroid® film.

Scan interpretation: The myocardial scans were analyzed and interpreted by two of us without knowledge of the clinical and angiographic findings. Because the first scan at rest was always the most accurate, qualitative and semiquantitative assessment was made as to whether there was delayed appearance of the radionuclide (that is, whether there were regions of low activity that had "filled in" by the second scan), and in the latter scans further changes in activity were observed. In early scans where the isotope was found to linger in the ventricular cavity, the later scans were carefully examined for topographic abnormality. The criteria for demonstrating collateral circulation were observation in the first scan of low counts in the proximal bed of a coronary artery with higher counts in the distal portions and a connecting "bridge" of activity to another arterial bed. The scans of patients with cardiomyopathy did not demonstrate delayed appearance time or a sequence of accumulation of activity. The abnormalities were manifested as small regions of high and low isotope activity uniformly distributed over the entire myocardium in a "salt and pepper" pattern.

Angiographic interpretation: Angiographic studies were performed in all patients with either the Sones or the Judkins technique. Selective right and left coronary angiograms were recorded on 35 mm film in several projections. Left ventriculograms were performed in the right anterior oblique projection after high pressure injection of contrast medium.

Results

Figure 1 demonstrates the sensitivity of the first resting serial scan completed within 4.5 to 5 minutes after administration of the isotope. Any abnormality demonstrated by the potassium-43 image in the first serial scan was a function of the appearance time of the isotope in the myocardium. Among the 85 patients to undergo scanning at rest with potassium-43, 74 had an abnormal first scan. Angiographic study indicated that 66 of the 74 had coronary artery disease, 4 had cardiomyopathy with no disease in the coronary circulation, 1 had a hypokinetic region in the inferior wall but a normal coronary angiogram, 1 had multiple muscular bridges over the left anterior descending coronary artery and 2 had no angiographically detectable disease.

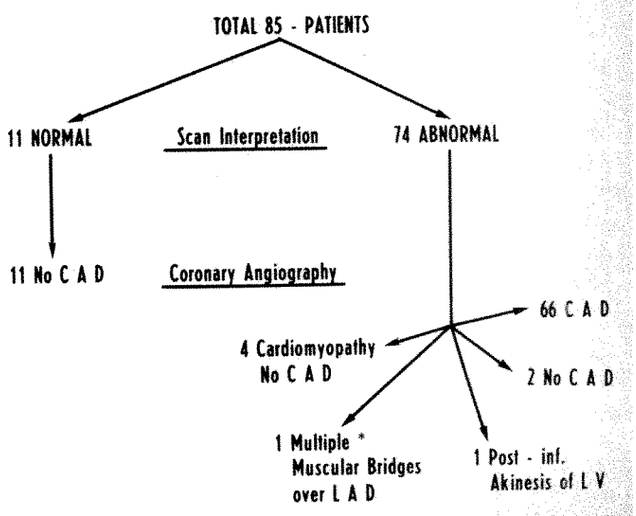


FIGURE 1. With respect to the presence or absence of coronary artery disease, this diagram compares the interpretation of the patient's first serial resting scans with the interpretation from contrast angiography (see text). CAD = coronary artery disease; LAD = left anterior descending coronary artery; LV = left ventricle; Post-inf. = posterior-inferior.

TABLE I

Combinations of Diseased Arteries Found by Coronary Arteriography in 32 Patients Who Participated in Both Exercise and Resting Scanning.

	Correct Scan Diagnosis				Incorrect Scan Diagnosis			
	Resting		Exercise		Resting		Exercise	
	Serial	Sum	Serial	Sum	Serial	Sum	Serial	Sum
Normal	3	3	3	3	...	...	...	...
LAD	...	...	1	...	1	1	...	1
RCA	2	2	1	1	...	...	1	1
LAD/LCF	...	...	...	...	2	2	2	2
LAD/RCA	3	3	3	1	...	...	...	2
RCA/LCF	...	1	...	1	2	1	2	1
Triple	19	19	19	19	...	...	...	...
Total	27	28	27	25	5	4	5	7
Percent correct	84.3	87.5	84.3	78.1	...	...	...	...

LAD = left anterior descending left coronary artery; LCF = left circumflex coronary artery; RCA = right coronary artery.

Table I shows the categories by involved arteries as determined with coronary angiography. The observers used the scans alone for classification. Although the scan results might be interpreted as abnormal, they were placed in the "incorrect" columns when they did not agree with the angiographic data as to the affected arteries or when the results were false positive. Double vessel disease in the left anterior descending and circumflex arteries appeared to be the most difficult to detect on scanning. The sum of the resting scans had the highest percent (87.5) of correct determinations because one combination of right coronary artery and left circumflex artery disease was detected when the scans were summed but missed in the serial scans at rest and during exercise. However, this table does not indicate the range of difficulty in interpretation of scanning, and the serial resting scans were the least difficult to interpret in most instances.

Representative Cases

Figure 2 exemplifies resting serial scans that were considered normal except for a slight elongation of the left ventricular silhouette.

Figure 3 shows the resting scans of a patient who had previous bypasses to the right coronary artery and the circumflex

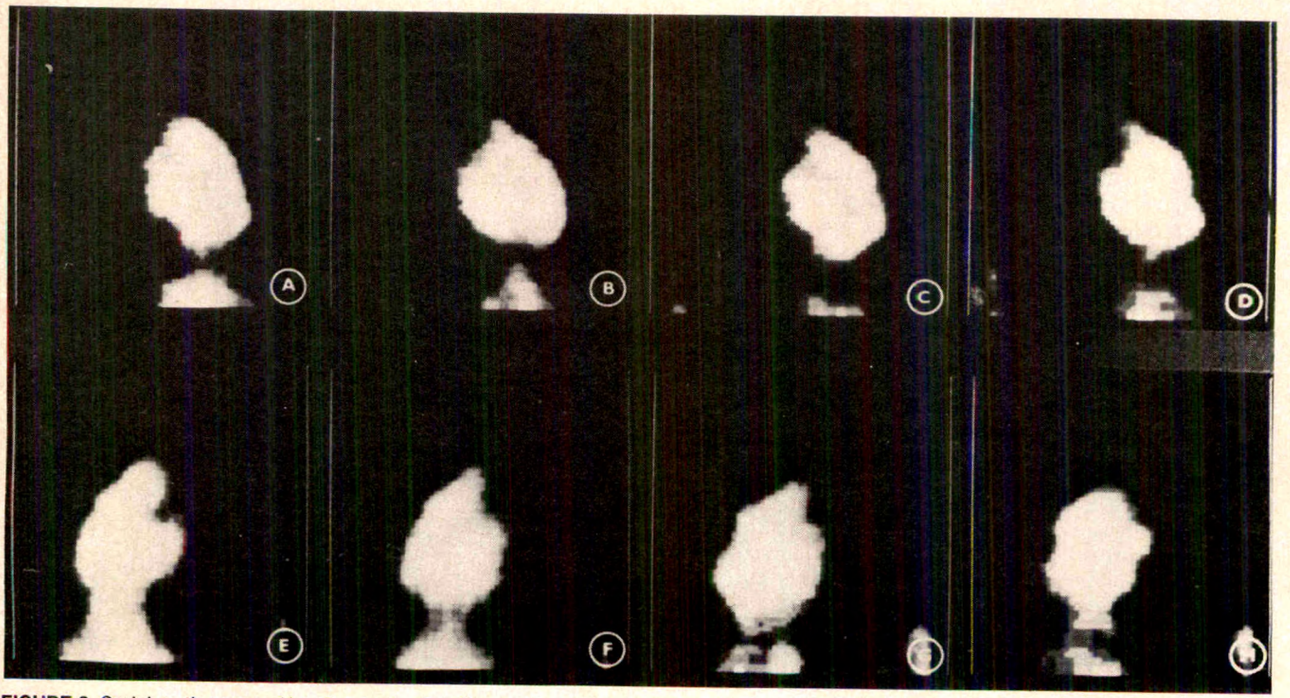


FIGURE 2. Serial resting scans (A to D anterior, E to H posterior) without significant uptake abnormalities from a 44 year old woman. Contrast angiography indicated irregular inferobasal left ventricular contraction with filling defects thought to be thickened and matted chordae tendineae. There were mild prolapse of the posterior mitral valve leaflet and moderately severe prolapse of the tricuspid valve.

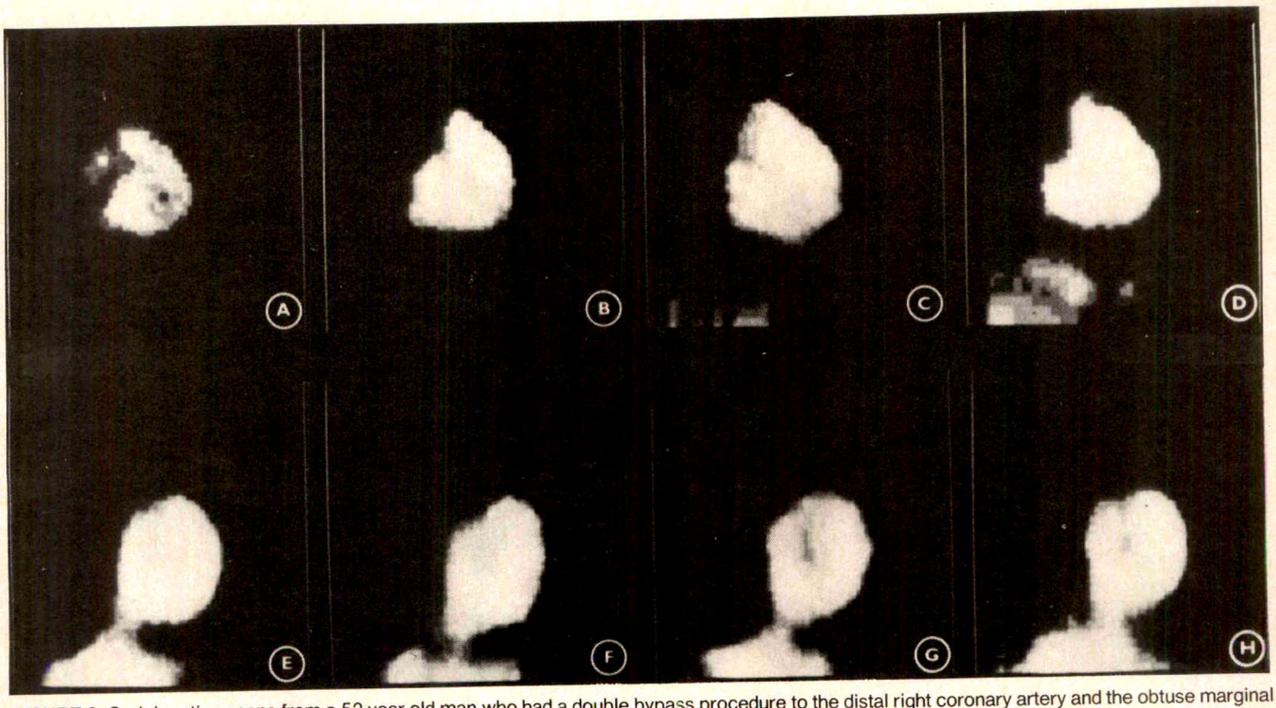


FIGURE 3. Serial resting scans from a 52 year old man who had a double bypass procedure to the distal right coronary artery and the obtuse marginal branch of the circumflex cornary artery 33 months previously. The four anterior scans (**A to D**) were followed by four left anterior oblique scans (**E to H**). The lower counts during the first scan (**A**) resulted from starting the radionuclide injection and scanning simultaneously. In scan **A** there is a small area of low counts that corresponds to the region supplied by the proximal right coronary artery, which was totally occluded before bypassing. Both grafts were patent when these scans were obtained.

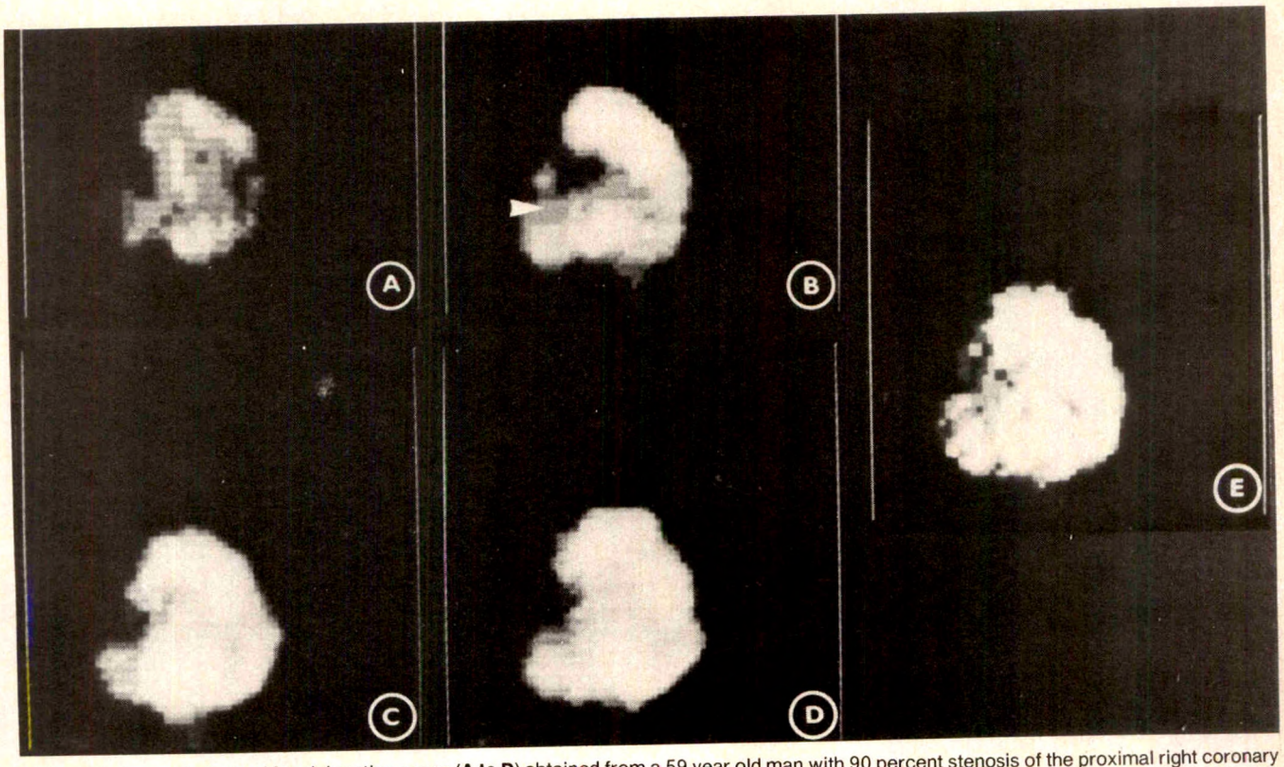


FIGURE 4. Four anterior rapid serial resting scans (**A to D**) obtained from a 59 year old man with 90 percent stenosis of the proximal right coronary artery and less than 50 percent occlusion of the circumflex coronary artery at the obtuse marginal branch. The arrowhead indicates a region of lower counts that occurred during the second scan (**B**). The regional difference in detected counts was not as evident in the display of the unaveraged sum (**E**) of the four anterior scans. (See text for explanation of the unaveraged sum image.)

branch of the left coronary artery. These scans were classified as abnormal. The first anterior view (A) shows very low counts (delayed appearance) in the region of the proximal right coronary artery and also the region supplied by the left anterior descending and circumflex arteries. Scan B demonstrates the delayed accumulation of the isotope in the area of the right coronary artery where there was a totally occlusive lesion that prompted a previous bypass to this artery. The fourth left anterior oblique scan (scan 3H) indicates slightly faster washout from the left anterior descending than from the left circumflex branch. Homogeneous myocardial counts were seen in all exercise scans from this patient. Coronary arteriography demonstrated patent bypasses.

Figure 4 shows the resting scan of the anterior aspect from a patient who had 90 percent stenosis of the luminal diameter of the proximal right coronary artery and more than 50 percent stenosis of the circumflex artery at the obtuse marginal branch demonstrated on coronary arteriography. In scan A there are regions with delayed appearance time; in scan B the arrow locates delayed accumulation of the isotope in the area perfused by the right coronary artery. The display of the sum of the unaveraged counts (scan E) was not as diagnostic although lower counts were shown in the area supplied by the right coronary artery. Because all the exercise scans in this patient were negative, the scanning diagnosis appears in the "incorrect" exercise column of Table I.

Figure 5 shows the resting scans from the anterior aspect of a man with triple vessel coronary disease. Coronary arteriography indicated (1) 50 percent occlusive lesions in both the proximal right coronary and left anterior descending arteries with an additional 50 percent occlusion of each artery one third of the distance along its course, and (2) more than 90 percent stenosis of the proximal circumflex artery and also one of its branches. There was also distal involvement with poor run off of the contrast medium and no evidence of collateral connections between arteries. The left anterior oblique scans from this patient (Fig. 6) were obtained immediately after the anterior views. Serial scans at rest and with exercise were indicative of triple vessel disease, but the stenotic left anterior descending coronary artery was not adequately demonstrated by the unaveraged sums of either the resting or exercise scans, especially from the anterior aspect

Figure 7 shows serial anterior resting scans thought to indicate triple vessel stenosis when angiography indicated only two vessel disease. However, one of the two vessels was the left main coronary artery. Late filling and collateral connnections were evidenced in the serial anterior resting scans (A to D) and regions of shifting radionuclide concentrations in the anterior and left anterior oblique resting scans (E to H). Such regional shifting was noted when coronary arteries had significant stenotic lesions. Coronary arteriography in this 51 year old man indicated luminal irregularity of the proximal right coronary artery giving off numerous collateral channels. Through these collateral vessels the contrast medium visualized the whole left anterior descending and circumflex arteries but not the left main coronary artery. The left anterior

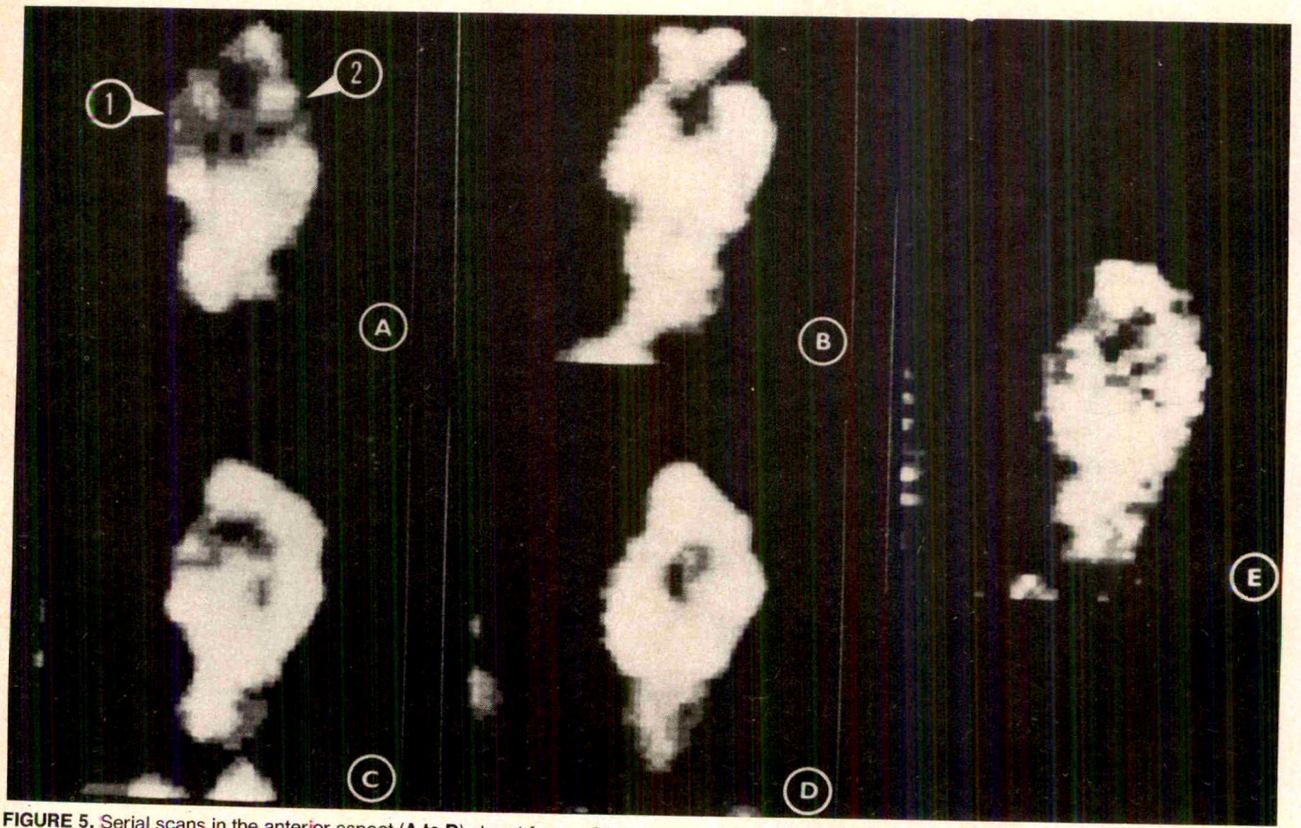


FIGURE 5. Serial scans in the anterior aspect (**A to D**) at rest from a 61 year old man with triple vessel disease (see text for description). Arrowhead **1** in the first scan (**A**) points out a low count region supplied by the proximal right coronary artery; arrowhead 2 indicates a similar region thought to be the result of decreased perfusion by both the left anterior descending and circumflex coronary arteries. Detected counts increased during the later scans (**B to D**) so that the deficiency was somewhat obscured in the unaveraged sum (**E**) of the scans.

descending and circumflex arteries were both normal in appearance, but a 90 to 95 percent stenotic lesion was demonstrated in the left main coronary artery just before its bifurcation. When the four anterior scans (Fig. 7, A to D) were summed (without 9 point averaging), the resulting single summed image (Fig. 8A) was abnormal but did not reveal the presence of collateral vessels. The summed image (Fig. 8B) of the left anterior oblique scans was also abnormal at the apex and proximal portion of the circumflex artery but was not indicative of delayed myocardial perfusion.

Figure 9 shows serial scans from a 58 year old man whose coronary angiograms and ventriculograms indicated triple vessel disease and a large anterior apical aneurysm of the left ventricle. There was total occlusion of the proximal right coronary artery and of the left anterior descending artery approximately one third of the distance down its course. The circumflex artery was more than 90 percent stenosed proximally with a similar obstruction halfway down its path. For the resting scans, the potassium-43 was not injected until the scanner had completed the first two lines of the first scan. Because the aneurysm allowed the radionuclide to linger in the left ventricular cavity, the approximate size and shape of the aneurysm were pictured in the first scan anteriorly and posteriorly (A and D) but were not seen in the following scans 9(B to C and E to F).

Discussion

Rationale of the rapid serial rescanning technique: When potassium-43 is injected rapidly intravenously in a single bolus dose, the tracer content of many organs, including the heart, rapidly reaches a high count level and remains high for many minutes despite the rapid fall in blood levels. It has been reasoned that the portion of the injected isotope that is taken up by the heart is indicative of the functional myocardial perfusion and, by counting the radionuclide (potassium-43) tissue deposition, an index of regional myocardial flow can be ascertained. For organ imaging in most laboratories, a single scan per viewing angle after a single bolus intravenous injection has been accepted as standard procedure. In experiments from our laboratory[7,8] using mongrel dogs, we showed that this method is not always adequate for myocardial imaging. Although the bolus injection-single scan technique will show very recent occlusion or severe disease of the coronary arteries, it will not indicate regions supplied by collateral flow or those supplied by diseased vessels that do not impair flow in the resting state. Myocardial regions supplied by stenotic arteries that allow normal resting flow could be demonstrated with the postexercise imaging technique.[1,2] Yet this technique also employs a single scan per viewing angle (10 to 15 minutes/scan). Another time delay of at least 5 minutes could be attributed to positioning the patient under the detector. We introduced the optimal serial rescanning technique when we found

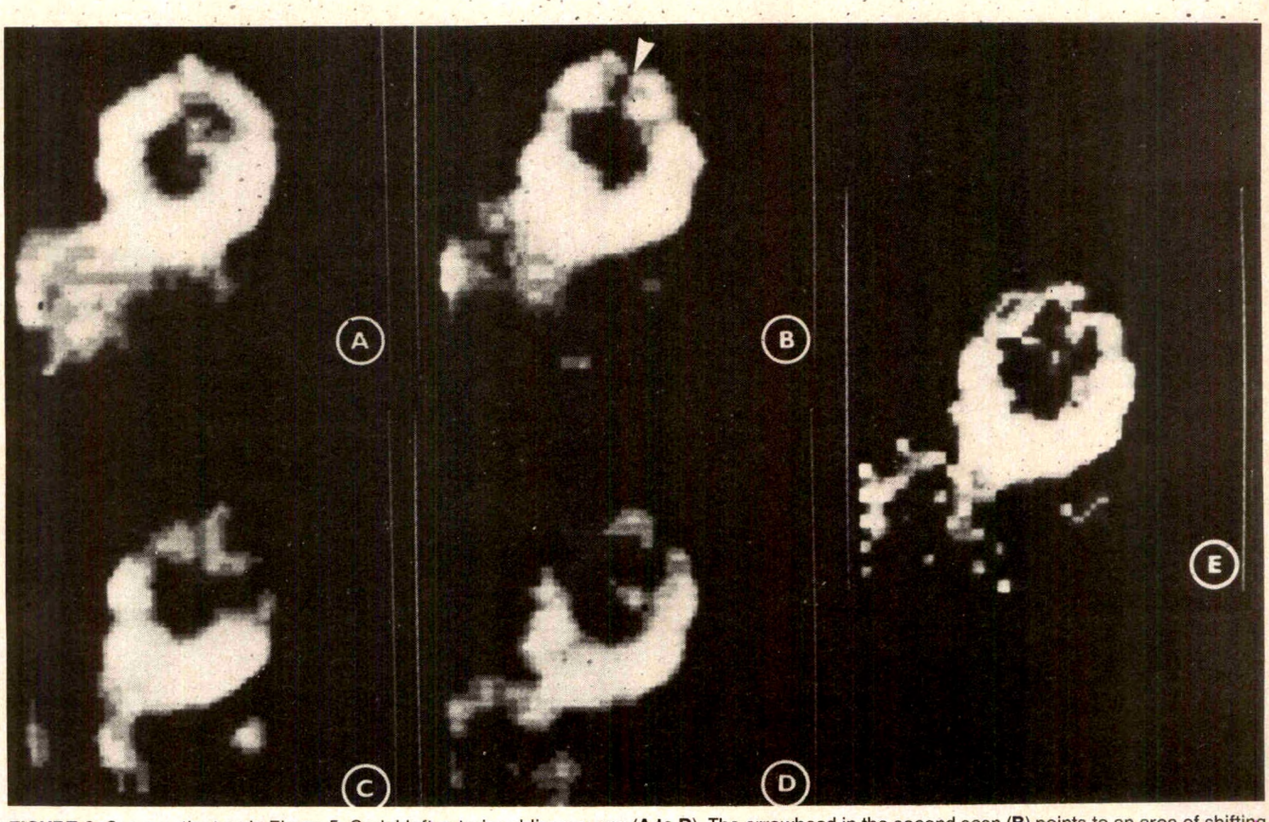


FIGURE 6. Same patient as in Figure 5. Serial left anterior oblique scans (**A to D**). The arrowhead in the second scan (**B**) points to an area of shifting counts and finally rapid washout (**D**). This region would usually be perfused by the proximal portions of the left anterior descending and circumflex coronary arteries. When the unaveraged counts were summed (**E**), the counts were still low in this region with an abrupt change in the contour of detected counts.

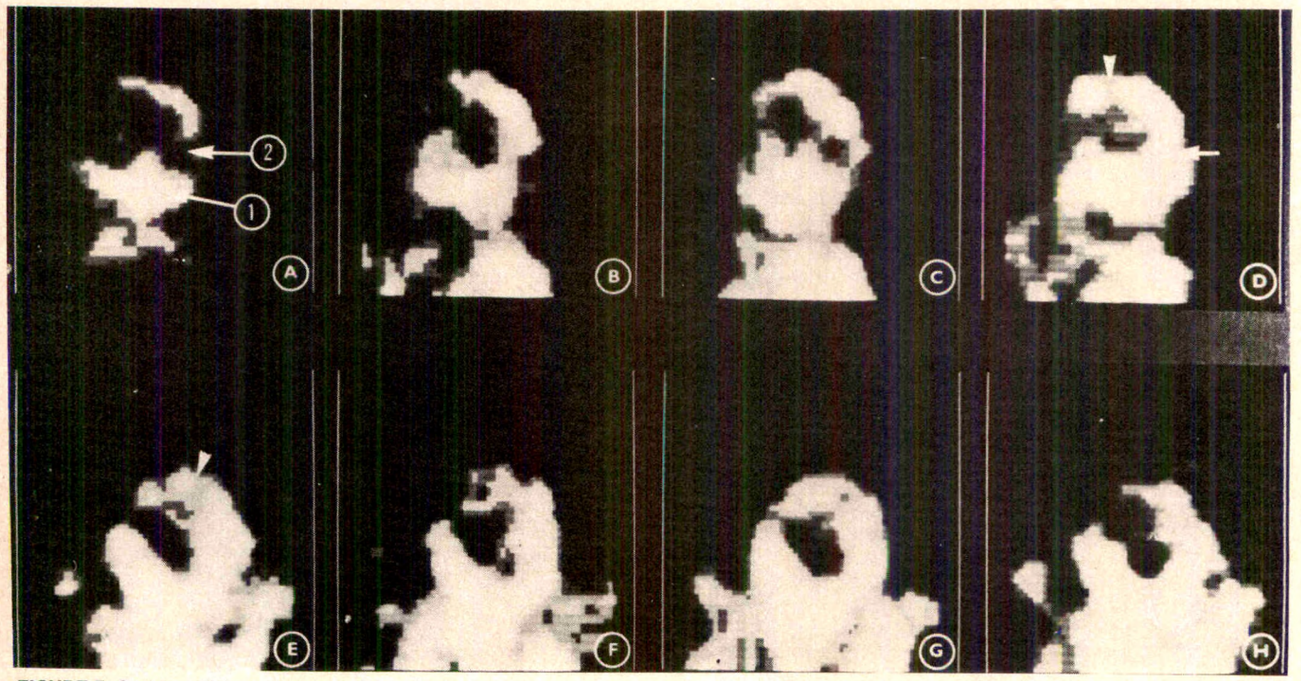


FIGURE 7. Serial resting scans from a 51 year old man. The scans were thought to demonstrate triple vessel disease, but angiography indicated significant stenosis of only the right and the left main coronary arteries (see text). Because the left main coronary artery branched into the circumflex and left anterior descending arteries, the scans do appear as though the three primary arteries were affected. The four anterior scans (**A to D**) are followed by the left anterior oblique scans (**E to H**). **Arrow 1** in the scan **A** points to the early radionuclide concentration in the area of the distal right coronary artery. **Arrow 2** points to a region that increased in concentration with time (**B to D**) and correlated well with some of the collateral vessels from the right coronary artery to both the left anterior descending and circumflex arteries that were evidenced by angiography. The **arrowhead** in scan **D** indicates an area of low activity in the region of the left coronary artery, whereas the arrow points to the same region indicated by **arrow 2** in scan **A.** In the first left anterior oblique scan (**E**) the **arrow** points to a shifting region of activity usually perfused by the proximal left circumflex branch.

that the optimal information indicative of myocardial perfusion patterns under resting conditions, with potassium-43 as the imaging agent, could be obtained when an image was recorded within 4 to 5 minutes after isotope administration.

Although in the normal heart muscle radioactive potassium regional appearance time for each major artery shows no delay and the sequence of accumulation and washout rate are relatively even over the entire myocardium, in the abnormal myocardium these time-dependent variables appear to be significantly altered. It is true that reduction of luminal diameter by as much as 90 percent would alter blood flow at rest little, if at all, provided some coronary vascular reserve were still present. In dogs with 70 to 85 percent stenosis in a major branch of the left coronary artery, we could not detect with rapid serial rescanning any perfusion defect at rest. However, when potassium-43 was given after the administration of a potent coronary vasodilator (dipyridamole), the myocardial region supplied

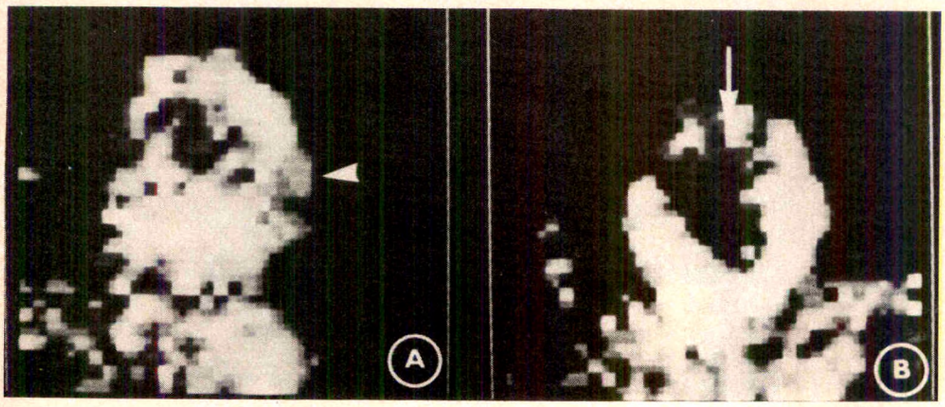


FIGURE 8. Same patient as in Figure 7. Without 9 point averaging, the four anterior scans of Figure 7 were summed into a single image (**A**). The **arrowhead** points to a region of low counts at the apex. A single display (**B**) was also obtained by summing the left anterior oblique scans; the **arrow** indicates a mottled count region supplied by the proximal left circumflex branch.

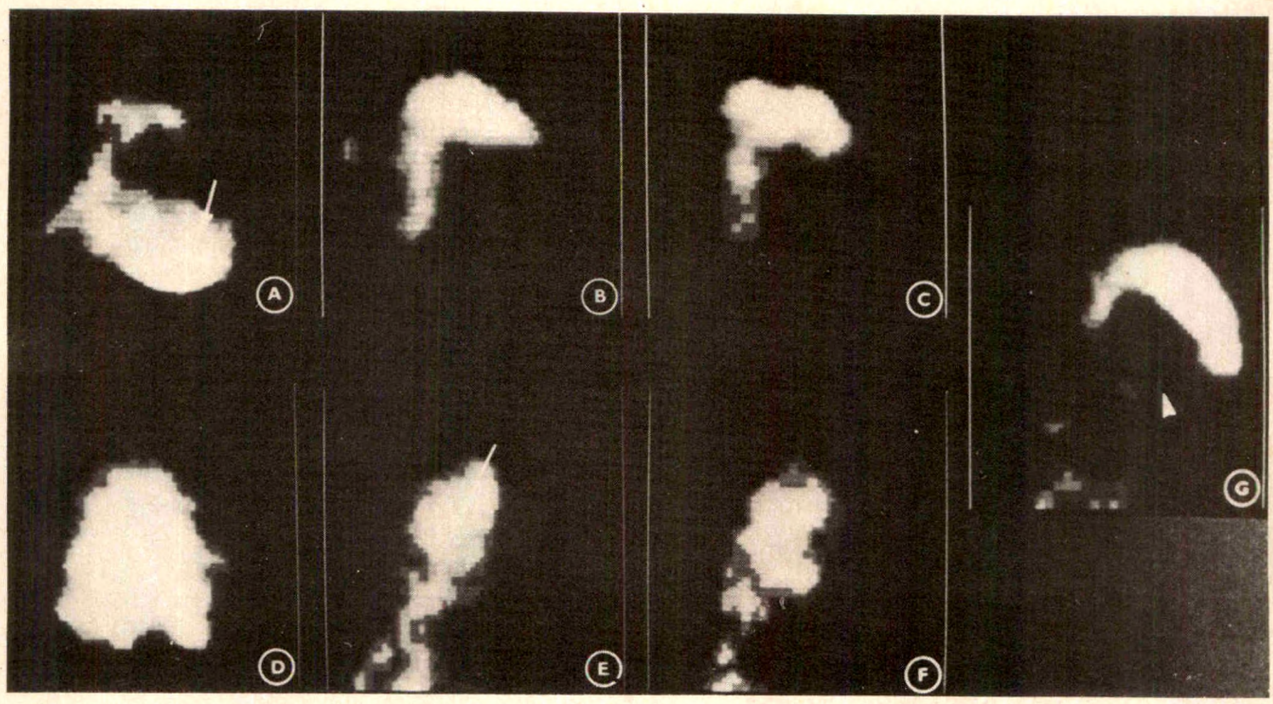


FIGURE 9. Anterior scans (**A to C**), posterior scans (**D to F**) and a single left anterior oblique scan (**G**) from a patient with triple vessel disease and a ventricular aneurysm (see text for angiographic data). The scanner was on the second scan line (from bottom as viewed) of the first scan when the potassium-43 was given intravenously. The **arrow** in the first anterior scan (**A**) points to the radioactivity that lingered in the left ventricle sufficiently long to be detected by the scanner. The size of this radioactive pool is indicative of the size of the aneurysm. In the second posterior scan (**E**), the **arrow** is along the bed of the circumflex branch whereas the **arrow** in the left anterior oblique scan (**G**) points to the low myocardial radioactivity count along the left anterior descending artery. The delayed appearance of the isotope (as seen in scans **A** and **B**) is indicative of an obstructive lesion in the region perfused by the circumflex artery. The scan was interpreted as indicating triple vessel disease.

by the stenotic vessel was clearly delineated.[9] Under normal conditions (when no coronary artery disease is present) the tone of the peripheral coronary vessels is the major determinant of the rate of total coronary blood flow. In the presence of coronary artery disease the situation is quite different. The tissue hypoxia causes the peripheral coronary resistance to decrease proportionately to the severity of the disease. Once the coronary reserve has been greatly decreased, the large vessel resistance becomes the flow-limiting factor. The effective resistance of the large vessels will therefore be the algebraic sum of the resistance of all lesions, however small, including minimal lesions with no significant luminal irregularity. Under these conditions the flow will be primarily determined by the magnitude of the perfusion pressure, assuming that there is no coronary flow reserve available. Moreover, the lumen of a single stenotic lesion is not solely responsible for alteration of blood flow under basal conditions; it is also possible that its length[10] and the number of lesions might influence the coronary hemodynamics in this region. If one assumes that there may be, distal to angiographically demonstrable lesions, other lesions in smaller vessels that are not discernible with contrast medium,[11] then the myocardial region that these vessels supply may demonstrate a deficit in resting flow. Therefore, by eliciting delayed regional myocardial potassium-43 appearance, a deficit in flow could be evidenced by rapid rescanning at rest.

Regional appearance time of potassium-43 as an index of high grade stenotic lesions or of collateral circulation: Transient ischemia has been detected during myocardial imaging at rest,[12] although in some cases coronary angiography failed to demonstrate hemodynamically significant lesions, and similar observations were recently reported[13] in studies using thallium-201, although the time sequence differed. In previous reports from our laboratory,[14] we demonstrated detection of hemodynamically nonrestrictive lesions in animals as well as in man with the continuously decreasing infusion technique.[14] Comparing the results obtained with the two techniques we found in both patients and animals that the first serial scan obtained within 4.5 minutes after a bolus dose of potassium-43 grossly reflects the appearance time of the isotope in the myocardium.[14] In animals with stenotic lesions of 85 to 95 percent or with poorly developed collateral vessels, studied after an intravenous bolus dose of potassium-43, the regional appearance time of the isotope appears to be delayed by nearly 5 minutes. In these cases the counts increase by the second scan to nearly normal values. Such a sequential regional accumulation of the isotope was never noted in the animals in which a major branch was rapidly ligated. Thus, we found that when

myocardial imaging is performed at rest, monitoring the regional appearance time (difference between the first and second scans) of the potassium-43 indicates lesions that restrict primary flow, whereas myocardial regions supplied by collateral circulation demonstrate a prolonged regional accumulation throughout scans one to four. In Figure 7, A to D, the region perfused by the left coronary artery demonstrates this sequential accumulation.

Disease involving the left anterior descending or circumflex artery, or both, was most difficult to identify because the first serial scans were performed in the anteroposterior position (Table I). Because of the topographic location of these arteries, their respective perfusion regions are superimposed and, by the time the patient was moved to the left anterior oblique position, the images were considered static except for early regional washout of the isotope from either myocardial district. We used this rapid washout as an index of impraired coronary flow, signifying an obstructive lesion that affected myocardial metabolism under resting conditions. It would be possible to obtain a left anterior oblique image and to follow the appearance time and sequence of accumulation of potassium-43 in that view if a detector were mounted at 45° on the present detecting equipment.

Clinical implications: From this study it is evident that in a clinical setting the rapid serial rescanning technique might prove more valuable than the present static imaging techniques. It will eliminate, in the majority of cases, the need for postexercise imaging and provide data for detecting an impaired regional myocardial metabolic state when the disease is inaccessible to coronary angiography. However, we must remember that the physical characteristics of potassium-43 and matching instrumentation are to a large measure responsible for the success with this technique. With thallium-201, the myocardial/background ratio reaches a maximum of 2 only after 15 to 20 minutes, which is the optimal time to begin scanning with it.[15] For potassium-43, this ratio is highest approximately 3 minutes after administering the bolus injection and decreases to about 4:1 after 15 minutes. These are opposing characteristics that may make duplication of the technique difficult with radionuclides other than potassium or rubidium.

Acknowledgment

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Thallium-201 Myocardial Perfusion Scintigraphy: Results of Standard and Multi-Pinhole Tomographic Techniques

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A new method of cardiac tomography was developed using a seven pinhole (5.5 mm diameter) collimator, a standard 37.5 cm diameter crystal Anger camera and a digital computer. Twelve planes spaced an average of 1.0 cm apart are reconstructed through use of a computer algorithm from a single stationary data acquisition. A comparison of the tomographic technique and standard (parallel-hole collimation) scintigraphy was performed using 65 patients (Group I), 23 without and 42 with angiographically demonstrated coronary arterial stenosis (greater than 70 percent luminal narrowing) who were undergoing stress thallium-201 imaging. An additional 7 normal subjects and 32 patients with coronary artery disease (Group II) underwent both tomographic imaging during stress and redistribution or rest. The tomographic images and standard anterior and left anterior oblique scintigrams were interpreted with use of a computerized program that determines maximal circumferential cardiac wall count densities and compares these profiles with normal limits obtained from the initially tested 23 subjects without coronary disease in Group I. Of these 23 persons, one had an abnormal standard scintigram and one an abnormal tomogram. Of the 42 patients with coronary disease in Group I, 31 had an abnormal standard scintigram and 40 an abnormal tomogram ($P < 0.05$). Of the 39 patients (Group II) undergoing tomographic stress and redistribution or rest imaging, none of the 7 normal subjects and 31 of the 32 (97 percent) with coronary artery disease had quantitatively abnormal stress images or greater than 20 percent segmental redistribution. These results suggest that this tomographic technique is both highly sensitive to and specific for the presence of coronary artery disease using stress thallium-201 imaging.

Myocardial perfusion imaging using radionuclide cations,[1] most recently thallium-201,[2–9] has gained clinical recognition as a test having 95 to 100 percent specificity, with abnormal exercise scintigrams occurring in about 75 percent of persons with coronary artery disease. Because myocardial imaging using the standard scintillation camera technique is hampered by superposition of proximal and distal cardiac walls and by the segmental nature of myocardial ischemia, emission tomography offers theoretical advantages. Although emission tomography was introduced as a scanning technique by Kuhl and Edwards[10] 15 years ago and as a scintillation camera technique by Muehllehner[11] 8 years ago, it has not been widely applied. In an attempt to utilize the theoretic advantages of tomographic myocardial perfusion imaging, our laboratory recently developed a new method of single photon emission tomography using a wide field scintillation camera, a seven pinhole collimator and a digital computer reconstruction algorithm. In contrast to the positron technique,[12] the method uses a standard scintillation camera. A computerized quantitative profile analysis program for interpretation of tomographic and standard images has also been developed. These techniques and their clinical application will be described.

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Methods

Tomographic collimator: A lead collimator was constructed with seven 5.5 mm diameter pinholes located 12.7 cm from the camera crystal, one placed centrally and six spaced evenly around a circle 6.35 cm from the center pinhole.[13] Lead septa were placed between adjacent pinholes to prevent overlapping of the seven projected images. The central pinhole has a conical 53° field of view that is perpendicular to the crystal face, whereas the peripheral pinholes have conical 45° fields of view that converge inward at 26.5°. Thus a 12.7 cm diameter volume is formed, within which emissive data project through all seven pinholes simultaneously onto seven independent crystal sectors, each viewing the volume from a different spatial angle.

Reconstruction process: In general, a sectional image is formed by planar tomography through superposition of multiple projections so as to focus data within the image plane and blur data proximal or distal to that plane. Other planes can be obtained by varying the superpositional relation. A refocusing process is frequently used by comparing the summed initially formed planes to the original projections. Differences between these views are used to correct the initial images so as to enhance their tomographic effect. Repetitive use of this refocusing process is the basis for iterative tomography.

Each seven pinhole study began with a single 750,000 count scintigraphic data acquisition using the pinhole collimator and an Ohio-Nuclear model Sigma-410 or Picker model Dyna Camera 4/15 wide-field scintillation camera. Data were stored on magnetic tape in frame mode and transferred to a Digital Equipment Corporation PDP-12 computer. The relative position of the seven views was established by imaging a radioactive point source centered 9 cm from the collimator. The seven views were then corrected for inherent distortion of pinhole sensitivity by dividing them by corresponding sheet-source flood images. As described, 12 initial tomographic planes were formed by appropriate superposition of the seven flood-corrected views so as to cause data focusing at approximately 1 cm intervals, at a distance of 9 to 20 cm from the collimator. Addition of the reciprocal images, followed by reciprocation of the sum, was used instead of simple addition.

A single step refocusing process was then accomplished. The initial tomographic planes were smoothed and weighted for tissue absorption, the most proximal plane being weighted three times as much as the most distal plane. A constant weighting was used throughout an individual plane. These planes were added to simulate the original viewing process, and the summed views were subtracted from the original views, resulting in seven difference views. With use of a predetermined variable combining factor, the refocusing process was finished by adding a proportion of the appropriately superpositioned seven difference views to each of the 12 initial planes. The final tomographic planes were both individually photographed from the computer display and stored on magnetic tape.

Exercise testing: One hundred four men referred to this institution for cardiac evaluation were informed of the nature of the procedure and consented to it. All underwent coronary angiography using the Sones technique and left ventriculography in the right anterior oblique projection. In 74 patients these studies revealed, on visual analysis, 70 percent or greater luminal stenosis of at least one major coronary artery, and in 32 of the 74 the left ventricular ejection fraction was less than 55 percent. All men underwent graded treadmill exercise testing performed in the fasting state according to the Bruce protocol.[14] No subject was receiving nitrates, digitalis[15] or propranolol. An adequate degree of exertion was considered achievement of 85 percent of age-predicted maximum heart rate (69 patients) or 1 mm of new S-T segment depression of a horizontal or downward sloping nature lasting at least 0.08 second (35 patients). Thirty seconds before the termination of exercise, 1.5 to 2.0 millicuries (mCi) of thallium-201 was injected intravenously.

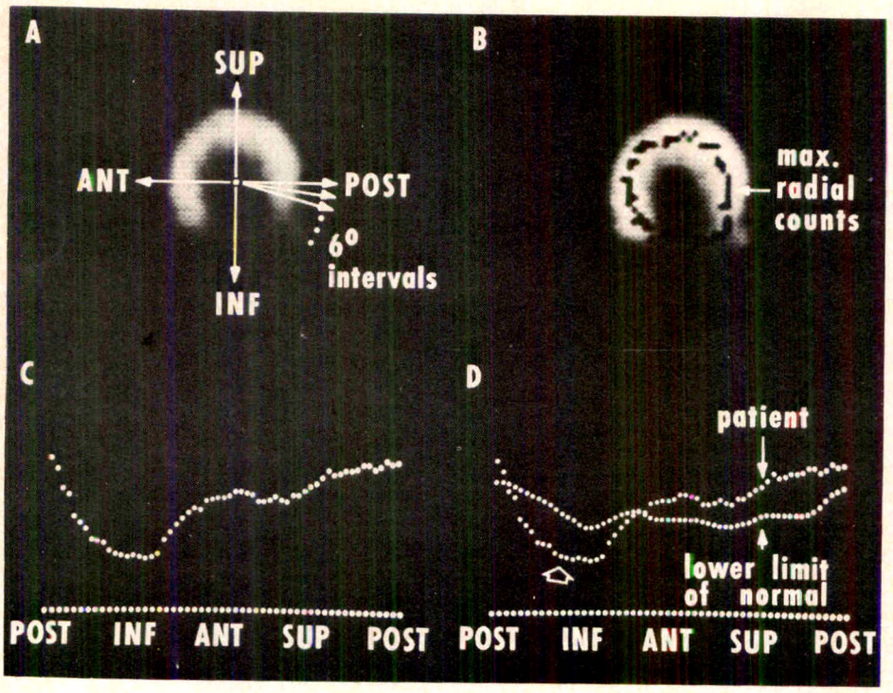


FIGURE 1. Quantitative interpretation of scintigrams: **A,** a myocardial perfusion scintigram undergoes computer analysis by determination of maximal pixel values along each of 60 radial lines at 6° intervals. The process is begun posteriorly and proceeds in a clockwise fashion. **B,** maximal (max.) radial pixel value locations are displayed. **C,** the maximal radial pixel values are plotted against their corresponding angular locations. **D,** the patient's circumferential profile is displayed along with the corresponding lower limit of normal. The inferior wall quantitative abnormality is marked by an **open arrow.** (See text for details.) ANT = anterior; INF = inferior; POST = posterior; SUP = superior.

Ten minutes later, in the first group of 65 men (Group I: 23 normal subjects, 42 patients with coronary artery disease) a single 40° left anterior oblique projection 750,000 count seven pinhole scintigram was obtained, followed immediately by 350,000 count anterior and 40° left anterior oblique projection standard scintigrams using a 2.5 cm thick parallel-hole (general all-purpose) collimator. In a second group of 39 men (Group II: 7 normal subjects, 32 patients with coronary artery disease) an initial 750,000 count seven pinhole scintigram was followed by either a redistribution pinhole scintigram 2 to 4 hours later (16 patients) or a resting seven pinhole scintigram after a second thallium-201 injection 1 week later (23 patients).

Quantitative profile interpretation: In an attempt to make the interpretation of the scintigrams objective, and to facilitate comparison of stress and redistribution images, each patient's two planar and three central left ventricular tomographic images were analyzed with the computerized method depicted in Figure 1 and previously reported by us[16] and by Meade et al.[17] Initially (Fig. 1A), the cardiac center is visually located. Then maximal pixel values are determined by computer along each of 60 radial lines that extend from the cardiac center spaced at 6° intervals. This process is begun in a posterior direction and proceeds in a clockwise fashion. Figure 1B shows the location of the maximal pixel values along the 60 radial lines displayed for operator confirmation. Subsequently (Fig. 1C), these maximal radial pixel values are plotted quantitatively in a circumferential fashion, being normalized to a maximal pixel value of 100. Using data obtained from the 23 persons in Group I with less than 70 percent coronary arterial stenosis, lower limits of normal were estab-

TABLE I

Summary of Scintigraphic and Angiographic Data (Group I)

	Coronary Stenosis <70%	Coronary Stenosis >70%		
		Total	With NLV	With LVD
Patients (no.)	23	42	24	18
Myocardial perfusion scintigram				
Abnormal standard	1 (4%)	31 (74%)	14 (58%)	17 (94%)
Abnormal tomographic	1 (4%)	40 (95%)	22 (92%)	18 (100%)

LVD = left ventricular disease (ejection fraction less than 55 percent; NLV = normal left ventricle (ejection fraction 55 percent or more).

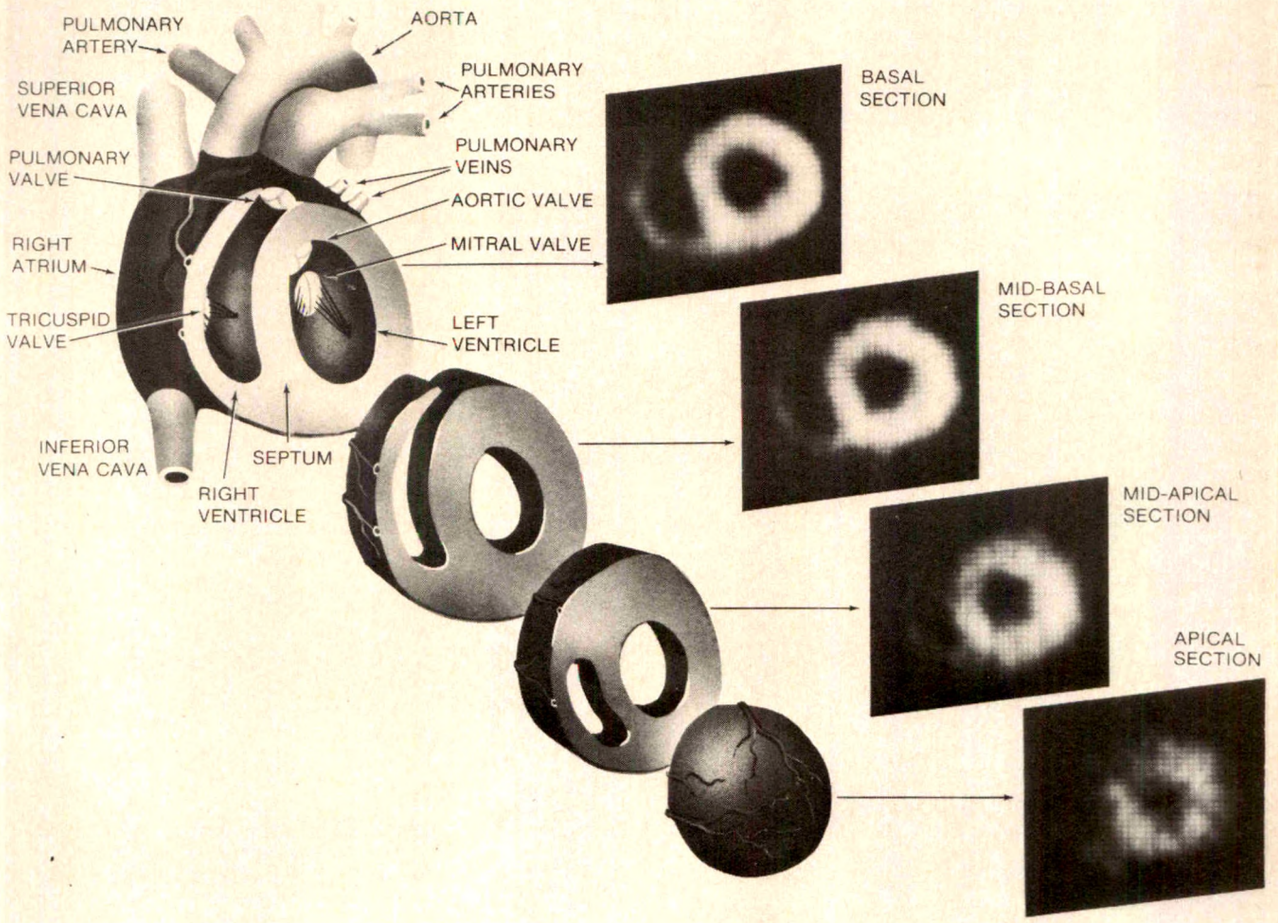


FIGURE 2. Anatomic orientation of the tomographic myocardial sections obtained with the multi-pinhole technique. Four of the 12 planes obtained from a patient with normal coronary arteries are displayed. Because of the pinhole collimation employed, apical data closer to the collimator are magnified to a greater extent, although all data within any single plane are magnified equally.

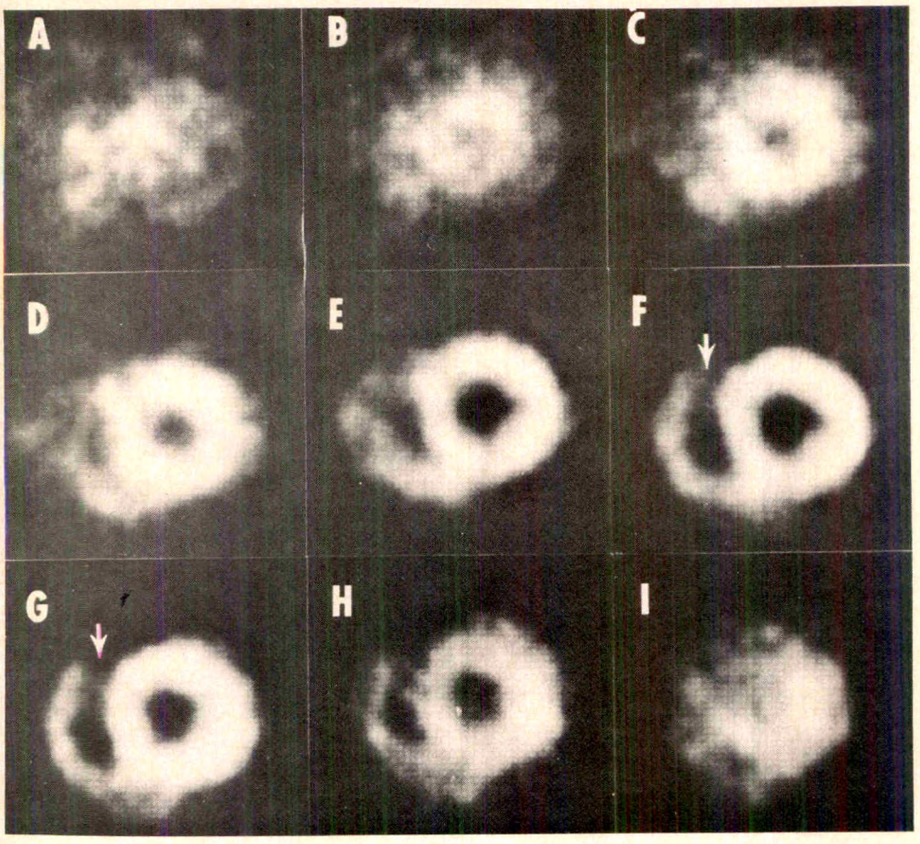


FIGURE 3. Stress thallium-201 tomograms from a patient with normal coronary arteries. Sections proceed from the cardiac apex (**A**) to the base (**I**). The discontinuity in the right ventricular myocardium (**arrows**) is thought to represent the region of the pulmonary valve.

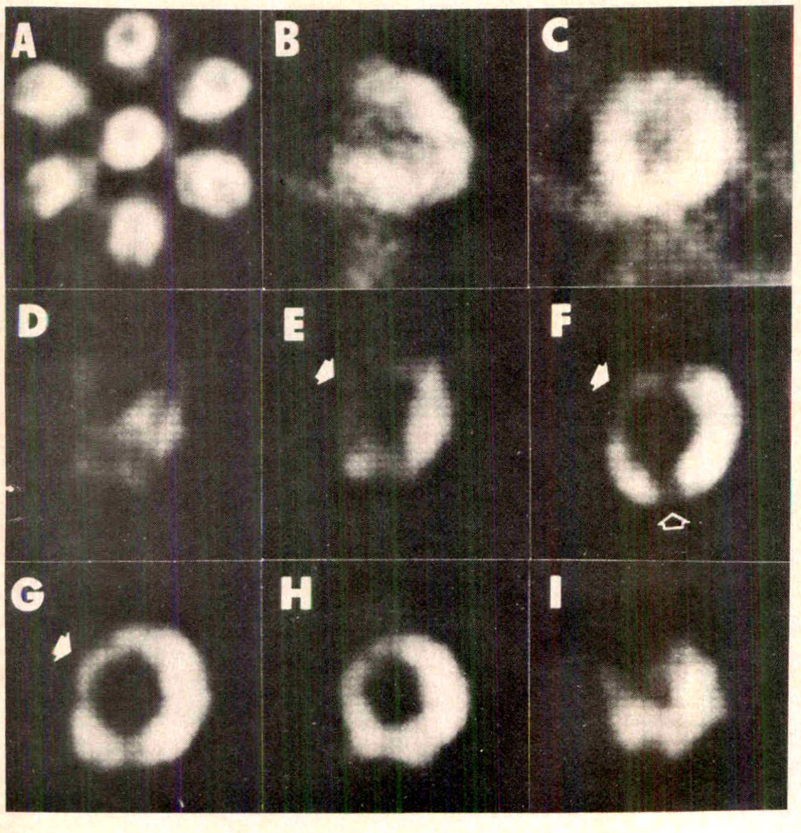


FIGURE 4. Composite pinhole image (**A**), standard anterior (**B**) and left anterior oblique (**C**) scintigrams, and tomograms from the cardiac apex (**D**) to the base (**I**) obtained from a patient with 90 percent stenosis of the left anterior descending coronary artery. An anterior wall defect is seen in **E** through **G** (**closed arrows**) and a normal apical defect is seen in **F** (**open arrow**).

lished for each of the 60 angular locations of the anterior and left anterior oblique standard images and for tomographic views of apical, central and basal regions. These values were established as mean values minus 2 standard deviations, followed by minor editing. In Figure 1D, the patient circumferential profile, plotted together with the lower limit curve for this 40° left anterior oblique control region tomogram, demonstrates the quantitative inferior wall defect (open arrow).

Because the observers lacked prior clinical experience, their visual interpretation of the tomograms showed significant inter observer variability, and this method of analysis was not employed.

Results

As previously reported,[13] planar full width, half maximal resolution (using 1 mm line sources of thallium-201) was found to be 1.0 cm 12.7 cm from the collimator, and depth resolution was found to be 1.5 cm. A simultaneous seven pinhole 750,000 count data acquisition requires about 10 minutes' time, and the new reconstruction algorithm we report requires about 5 minutes' time to perform versus approximately 1 hour for the iterative method previously reported. Quantitative profile image analysis requires 2 minutes' time per image analyzed.

Standard versus tomographic imaging (Group I) (Table I): As shown in Figure 2, tomographic images are reconstructed in planes perpendicular to the heart's long axis. A study obtained from a normal person is shown in Figure 3. When individual patient maximal count profiles were compared with the lower normal limit values, two studies (one standard and one tomographic) among the 23 persons in Group I without significant coronary disease were found to be abnormal. Among the 42 patients with coronary artery disease in Group I, 31 standard studies (74 percent) and 40 tomographic studies (95 percent) were found to be abnormal. Among the two subgroups with coronary artery disease, the superiority of the tomographic technique was most evident among the 24 patients in Group I with

TABLE II
Summary of Scintigraphic and Angiographic Data (Group II)

	Coronary Stenosis <70%	Coronary Stenosis >70%		
		Total	With NLV	With LVD
Patients (no.)	7	32	18	14
Abnormal tomographic stress myocardial perfusion scintigram	0 (0%)	30 (94%)	16 (89%)	14 (100%)
>20% redistribution by tomography	0 (0%)	22 (69%)	15 (83%)	7 (50%)
Abnormal stress myocardial perfusion scintigram >20% redistribution	0 (0%)	31 (97%)	17 (94%)	14 (100%)

LVD = left ventricular disease (ejection fraction less than 55 percent); NLV = normal left ventricle (ejection fraction 55 percent or more).

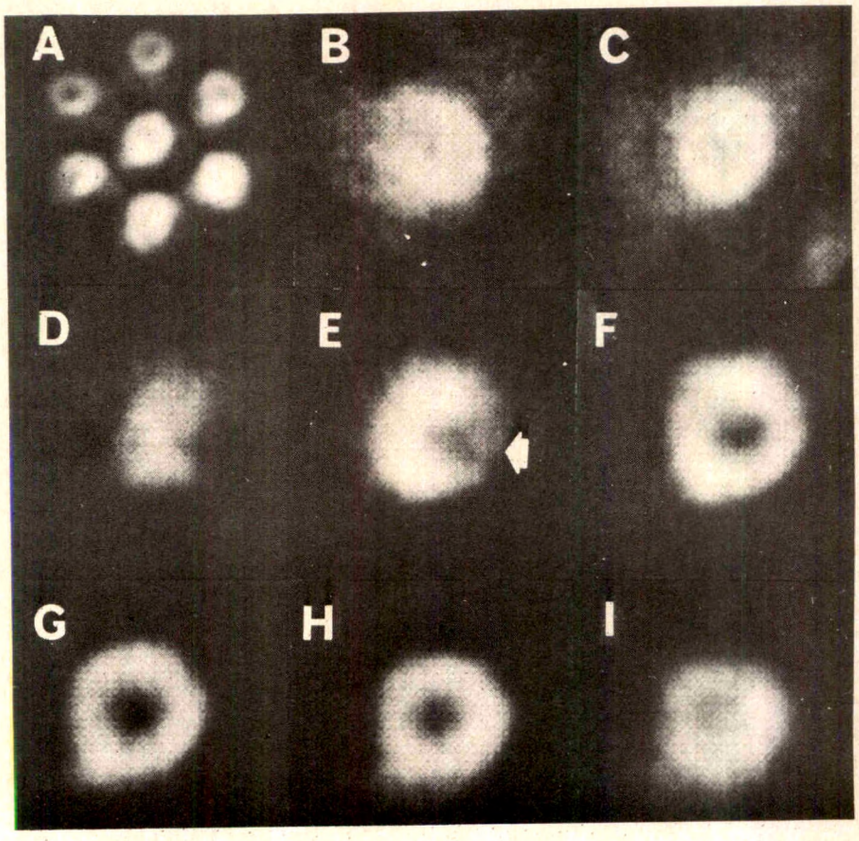


FIGURE 5. Composite pinhole image (**A**), standard anterior (**B**) and left anterior oblique (**C**) scintigrams, and tomograms from the cardiac apex (**D**) to the base (**I**) obtained from a patient with three vessel coronary artery disease. A posteroapical defect is seen in **E** (**arrow**).

a normal ventriculogram, the number of abnormal tests increasing from 14 (58 percent) with standard imaging to 22 (92 percent) with tomographic imaging (Fig. 4 and 5). All 18 patients in this group with an abnormal ventriculogram had an abnormal tomogram, whereas 17 (94 percent) had an abnormal standard image. Chi square analysis showed that tomographic data correlated better with coronary angiographic findings than did the standard imaging results ($P < 0.05$).

Stress versus redistribution or resting scintigrams (Group II) (Table II). None of the seven patients in this group with insignificant coronary artery disease had either an abnormal stress tomogram or a greater than 20 percent regional change between the stress and the redistribution or resting quantitative circumferential profiles. Of the 32 patients with coronary artery disease in this group, 30 (94 percent) had an abnormal stress tomogram and 22 (69 percent) had more than 20 percent regional redistribution. Overall, 31 (97 percent) had abnormal stress or regional redistribution data.

Discussion

Although the tomographic technique presented is conceptually similar to other tomographic methods, the use of a stationary large field Anger scintillation camera to obtain multiple simultaneous views has not previously been described. Coded aperture techniques obtain nonindependent overlapping views, and the rotating collimator technique obtains nonsimultaneous views. The 12 cm diameter field of view has been found sufficient for all hearts studied to date, although accurate positioning is necessary and the right ventricle cannot always be included. Total imaging and computer reconstruction require approximately 15 minutes. The rapidity of the reconstruction algorithm is largely due to the single refocusing step used, which allows maximal correction of the initial tomographic planes in a single step in contrast to standard iterative techniques.[18–20] Additionally, due to the use of planar rather than axial tomography, tissue absorption correction can be easily approximated.

Comparison with other scintigraphic methods: The results of standard myocardial perfusion scintigraphy, which showed abnormalities in 4 percent of persons with normal coronary angiograms and 74 percent of patients with coronary artery disease, agree closely with the data of Bailey et al.[4] and Ritchie et al.,[8] who found abnormal scintigrams in 0 and 4 percent of normal persons and 75 and 76 percent of patients with coronary artery disease, respectively. The similar sensitivity values obtained suggest comparable methodology. Botvinick et al.[21] and Ritchie et al.[9] found sensitivity values of 85 percent and 78 percent, respectively, comparing scintigraphy with angiography, but had 11 and 12 percent, respectively, falsely abnormal images. In keeping with the greater ability of tomography to visualize segment detail, 95 percent of patients with coronary disease had abnormal tomographic scintigrams with exercise. Such improvement in sensitivities of the tomographic technique is consistent with the abstracted data of Cantez et al.,[22] which suggested improvement in thallium-201 imaging sensitivity with the addition of tomographic technique. Recently, Nishiyama et al.[23] measured the resolution and sensitivity in detection of experimental infarction of pinhole, high resolution parallel hole and converging collimators. Their data suggested that use of the pinhole collimator resulted in an approximate threefold increase in resolution of thallium-201 images compared with high resolution collimation. Moreover, use of a pinhole collimator increased the rate of detection of experimental infarction to more than 90 percent compared with the 75 to 80 percent rate of a high resolution collimator. A third factor that may add to the improved detection of coronary artery disease with our technique is its ability to obtain seven views within approximately 10 minutes. The large number of views may facilitate detection of a perfusion defect through its visualization in a more favorable projection. Comparably performed by standard imaging technique, seven views would require more than an hour's imaging time with accompanying image degradation due to redistribution. Examples of quantitatively and visually falsely normal standard scintigraphy coupled with quantitatively and visually abnormal tomography are shown in Figures 4 and 5.

Possible limitations: A possible limitation of our study is the performance of tomography before standard imaging, allowing a period of 10 to 15 minutes during which thallium undergoes redistribution.[7,24] Two factors suggest that this is not an important issue. First, as mentioned before, the similar sensitivity values for standard imaging compared with those previously reported suggest that this delay has not significantly altered these images. Second, directly measured rates of thallium-201 redistribution in patients in Group II suggest that less than 5 percent redistribution occurs in this 10 to 15 minute period, thereby altering the standard views quantitatively to a minor degree.

In summary, the new tomographic and quantitative profile analysis techniques presented result in high specificity and sensitivity rates for the detection of coronary artery disease using thallium-201 myocardial perfusion imaging. These techniques can be rapidly performed with generally available nuclear medicine resources.

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Photokymography: A Noninvasive Method of Detecting Ischemic Segmental Myocardial Wall Motion Abnormalities

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The photokymograph is a new and simple noninvasive device for assessing epicardial segmental myocardial wall motion utilizing cardiac fluoroscopy and image intensification. The validity of this technique in detecting wall motion changes occurring with ischemia was assessed in seven closed chest dogs undergoing acute balloon occlusion of the left circumflex coronary artery. Acute occlusion resulted in a prompt change in the analog signal of the photokymogram, characterized first by a decreased systolic inward motion and late systolic outward movement that later became akinetic and dyskinetic. Systolic amplitude decreased 18 ± 7 percent (mean ± standard error of the mean) within 5 seconds of occlusion and progressed to systolic outward motion (−106 ± 24 percent) at 2 minutes. The time course and type of morphologic changes observed after occlusion were similar to those previously described using invasive methods. Furthermore, such changes preceded electrocardiographic S-T segment elevation. These data suggest that photokymography is a sensitive technique for noninvasive detection of acute ischemic segmental wall motion abnormalities and holds promise as a simple method of detecting ischemic heart disease in man.

Abnormalities of left ventricular segmental wall motion are sensitive and specific markers of ischemia. Recent animal studies have shown that abnormal segmental wall motion, induced by acute regional myocardial ischemia, precedes electrocardiographic S-T segment changes[1–5] and that these abnormalities are readily precipitated by both exercise[6] and cardiac pacing[7] in the presence of partial coronary stenosis. Similarly, exercise stress studies have indicated that segmental wall motion analysis contributes significantly to improved diagnostic accuracy with stress testing.[8] However, the main noninvasive techniques currently in use—echocardiography,[9,10] cardiokymography[11–13] and gated blood pool scintigraphy[8]—have important limitations when used to diagnose ischemic heart disease. Echocardiography is difficult to perform after exercise, cardiokymography is limited to analysis of anterior segmental wall motion and technetium-99m ventriculography cannot detect beat to beat changes in wall motion. Additional methods of objective assessment of regional contraction abnormalities might permit more accurate detection and evaluation of coronary artery disease in man.

Cardiac fluoroscopy is one technique that has received intermittent attention during the past 50 years as a method of assessing cardiac performance. As early as 1912, attempts to assess regional cardiac wall motion were made using roentgenkymography.[14] In the 1930's, this approach was further developed using a photosensitive tube attached to the fluoroscopic screen and placed over the cardiac silhouette during fluoroscopy.[15] Roentgenkymography and electrokymography were then widely applied to the study of cardiac pulsations in patients with valvular heart disease and acute myocardial infarction.[16–19] However, these

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techniques were less applicable to detection of stress-induced changes in segmental wall motion, primarily because the clinical need for such methods was limited and secondly because the devices employed were expensive and cumbersome.

In this study we utilized improved electronic technology to reassess the possibility of effectively applying cardiac fluoroscopy to the assessment of segmental wall motion. Specifically, we attempted (1) to construct a simple, inexpensive method of analyzing segmental wall motion as recorded with fluoroscopy, and (2) to determine if the method was sufficiently sensitive for noninvasive detection of acute ischemic segmental wall motion abnormalities.

Method

The instrument: The photokymograph consists of a silicon photoelectric cell (5 by 20 mm) that is placed directly over a boundary on the image of interest on a video monitor. The cell provides an electric current linearly proportional to the average level of illumination over this area. This current is converted to a voltage that is amplified and recorded as an analog signal. The rapid time response of the photoelectric cell is such that the unfiltered signal contains a 60 hertz flicker artifact due to the inherent design of the television format. The wave form is therefore passed through a low pass filter with a slope of 24 decibels/octave to remove this artifact. The overall frequency response is 0 to 12 hertz (+0, −3 decibels) with a negligible phase shift below 10 hertz. A block diagram of the system is illustrated in Figure 1.

Experimental procedure: Seven mongrel dogs were premedicated with morphine (1.5 mg/kg body weight subcutaneously), and anesthesia was induced with sodium pentobarbital (25 mg/kg intravenously). Ventilation was artificially maintained using tracheal intubation and a Harvard pump respirator. The dogs were positioned on their right side under an image intensifier fluoroscope to allow observation of both the anterior and posterior walls. Fluoroscopic X-ray factors ranged from 0.4 to 0.6 milliamperes and 70 to 75 kilovolts. The electrocardiogram (chest lead and leads III and aVF) was monitored continuously. No. 7F polyethylene catheters were introduced by way of the femoral arteries into the left ventricle and aorta. Pressure was recorded by Statham P23Db transducers. A no. 2F balloon catheter was then introduced by way of the carotid artery into the left circumflex or anterior descending coronary artery. A 5 second fluoroscopic image of the cardiac silhouette obtained with respiration stopped at end inspiration was recorded on videotape simultaneously with the electrocardiogram and left ventricular pressure. The coronary balloon was then inflated and occlusion maintained for 2 minutes. Fluoroscopic recordings were repeated at 5, 10, 30, 60 and 120 seconds after occlusion and 30 seconds after release. Total fluoroscopic time for each dog was approximately 25 to 30 seconds (4 seconds per imaging interval). The video tape images were then replayed on a 12 inch (30.48 cm) television monitor. The contrast and brightness were previously adjusted and not altered during playback.

One to four photokymographic photoelectric cell transducers were positioned on the face of the monitor at the border of the cardiac silhouette in the region of the posterior segment and apical or anterior segment, or both, of the left ventricle. The analog epicardial photokymographic signals were amplified on an Electronics for Medicine model VR6 physiologic recorder together with the electrocardiogram and aortic and left ventricular pressure at a paper speed of 100 mm/sec. Because the video tape system utilized does not contain provision for absolute stabilization of brightness, the resultant photokymographic signal could not be calibrated from one dog to another. The data were therefore reduced by analysis of relative amplitude.[13] Each wave form was normalized to maximal amplitude. The period of ejection was defined as the period between the point corresponding to the upstroke of the aortic pressure wave form and the dicrotic notch. The amplitude of the photokymographic wave form during the ejection period was then expressed as a percent of total amplitude.

Statistical analysis was performed by analysis of variance for repeated measures and the Newman-Keuls test.[20]

Results

Normal tracing: A typical photokymogram obtained simultaneously over four regions of the normally contracting left ventricular silhouette is illustrated in Figure 2. Except at the cardiac apex, each wave form is characterized by a major downward deflection, repre-

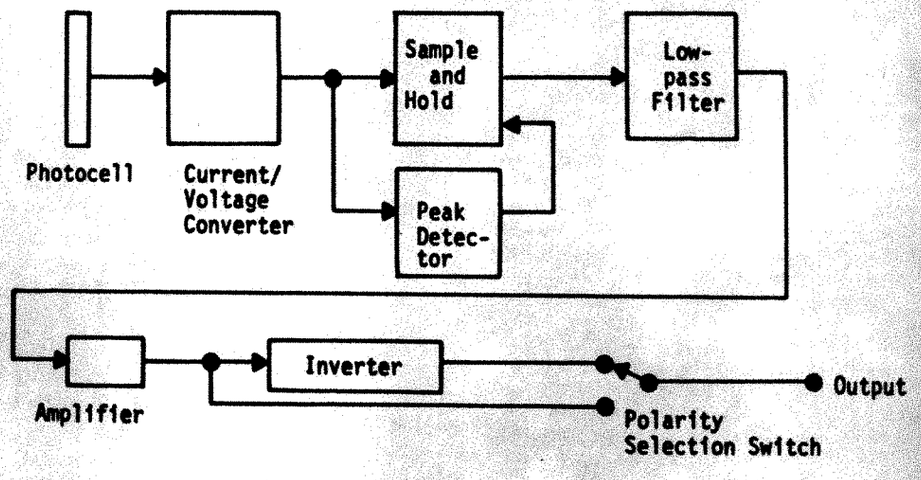


FIGURE 1. Circuitry of the photokymograph in block diagram form. The photoelectric cell generates current proportional to illumination. A current to voltage converter provides suitable voltage level. The peak detector, together with the sample and hold circuit, removes the majority of flicker present in the cine and video images; the low pass filter removes the remainder. The polarity selector switch, together with the inverter, allows use with both cine and fluoroscopic images.

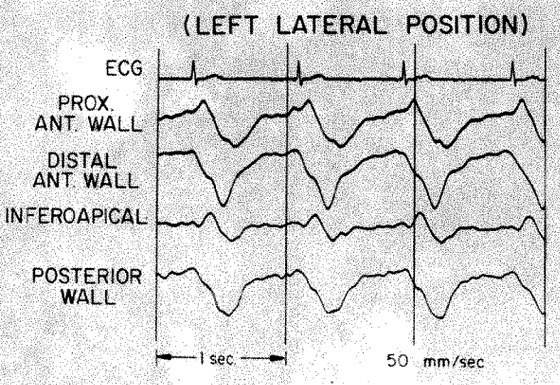


FIGURE 2. Simultaneous multiple photokymograms of the normally contracting ventricle. **From top to bottom:** electrocardiogram (ECG, lead III), photokymogram of the high proximal (PROX.) anterior (ANT.), the distal anterior, the inferoapical and the posterior regions of the left ventricular wall. With the exception of the apical region, the predominant systolic motion is inward. The apical photokymogram shows an initial outward movement due to total cardiac displacement during contraction.

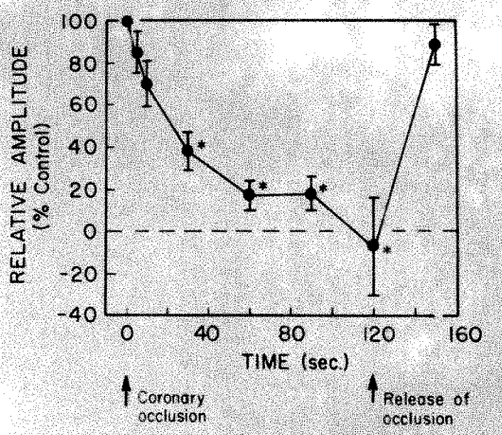


FIGURE 4. Time course of regional ischemic dysfunction in seven dogs as detected with photokymography. There is a marked decrease in normalized systolic shortening during the first 30 seconds of coronary occlusion and a prompt return to normal values within 30 seconds of release. Each symbol represents the mean value ± standard error of the mean for all seven dogs. Significant differences ($P < 0.01$) from control value are indicated by asterisks.

senting an increase in absolute brightness and, therefore, inward motion of the cardiac border across the face of the photoelectric cell. At the cardiac apex, an outward motion representing a shift of the heart along its long axis was often recorded.

Effects of coronary occlusion: Figure 3 illustrates a typical example of the change in fluoroscopically recorded segmental wall motion after coronary occlusion. This pattern is characterized by the development of an outward movement in late systole at 30 seconds that progressively encroaches on systolic ejection until the segment becomes virtually akinetic by 120 seconds.

Figure 4 illustrates the mean response (± standard error of the mean) for the temporal sequence of reduction in systolic inward motion after coronary occlusion in all seven dogs. Within 5 seconds of occlusion, systolic inward motion decreased 18 ± 7 percent from the control value and continued to decrease progressively until, at 2 minutes after occlusion, systolic outward motion predominated (mean − 105 ± 24 percent). Control values returned within 30 seconds of release of the occlusion in six of the seven dogs. The time course of reduced systolic shortening was exponential in nature and corresponded to that previously observed using invasive methods (Fig. 5).

Electrocardiographic changes: In comparison with the rapid appearance of changes in segmental wall motion after coronary occlusion, changes in the electrocardiographic S-T segment were slower to appear. Unlike the regional wall motion changes, S-T segment

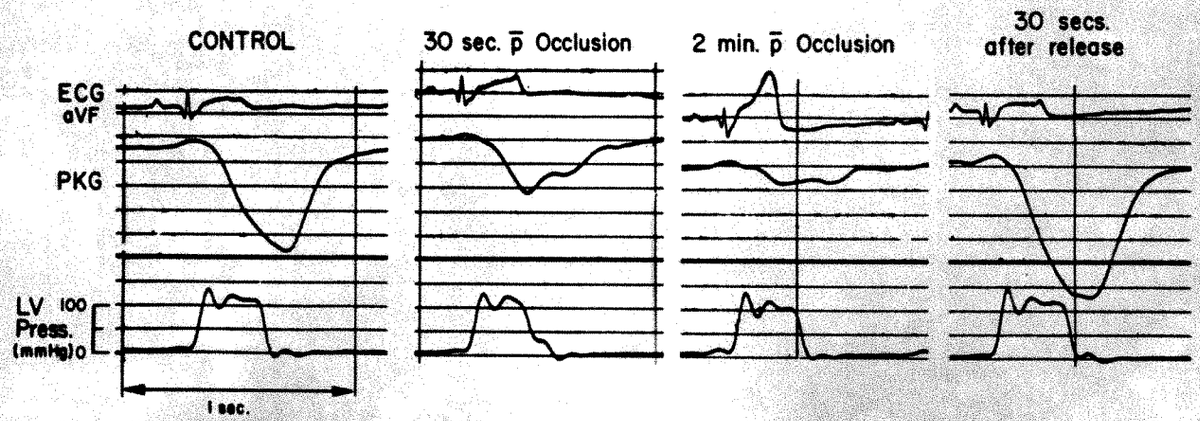


FIGURE 3. Representative example of the photokymogram (PKG) of the posterior left ventricular wall before and after occlusion and after release of the circumflex coronary artery. The magnitude of systolic inward motion decreases, and a late systolic outward movement develops over the period of occlusion until a nearly akinetic tracing is obtained at 2 minutes after occlusion. After release of occlusion, there is prompt return to control values. ECG = electrocardiogram; LV Press = left ventricular pressure; p̄ = post.

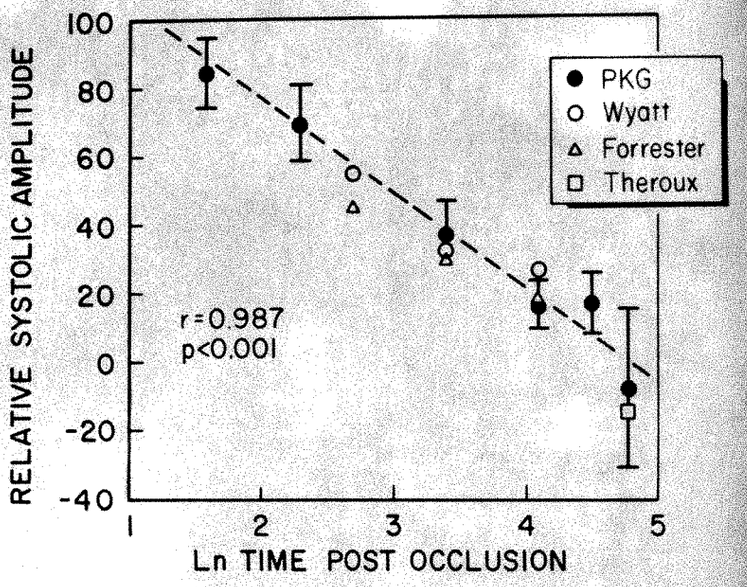


FIGURE 5. Time course of regional ischemic dysfunction. The data from the seven dogs whose data are shown in Figure 4 are plotted logarithmically (Ln). Note the close linear relation among the variables and the agreement of the photokymographic (PKG) data from this study (**closed circles**) with data derived from directly implanted gauges (Theroux et al.[3] [**open squares**], Wyatt et al.[5] [**open circles**] and Forrester et al.[25] [**open triangles**]). p = probability.

changes were not observed in all dogs and became apparent only after 15 to 30 seconds of occlusion. Moreover, these changes persisted longer than the reduction in systolic shortening, control values returning only 60 to 90 seconds after release of the occlusion.

Discussion

Evaluation of segmental myocardial wall motion has recently become an important method of noninvasive diagnosis of ischemic heart disease. When assessed with cardiokymography[11,21] and gated blood pool scintigraphy,[8] stress-induced abnormalities in regional wall motion were reported to provide a highly accurate means of diagnosing clinical coronary artery disease; levels of sensitivity of 70 to 90 percent and of specificity of 90 to 95 percent were shown. Such observations are not new. Exercise-induced outward systolic motion was observed using kinetocardiography,[22] and similar ischemic wall motion abnormalities at rest were extensively studied with roentgenkymography[16] and electrokymography.[17–19]

Although photokymography is similar to electrokymography and roentgenkymography, it is a relatively low cost electronically improved technique, potentially applicable to detection of cardiac pacing- and exercise-induced wall motion abnormalities in man. A preliminary example of such use is illustrated in Figure 6. If, as found in previous animal studies,[6,7,23] the abbreviated ejection time at higher heart rates does not materially influence the pattern of systolic shortening, then these data suggest that stress-induced regional ischemic dysfunction develops in the face of partial coronary occlusion. In this application, the anterior wall is easily recorded in human beings. However, in the animal laboratory, the dog's right ventricle often overlies the fluoroscopic anterior left heart border. For this reason we more often chose to evaluate the photokymogram over the posterior wall during occlusion of the left circumflex coronary artery. Parallel angiographic and length gauge studies after occlusion of the left anterior descending coronary artery performed in our laboratory[5,24] revealed similar uniform regional changes anteriorly.

Comparison with other methods: The alterations in segmental wall motion after coronary occlusion observed in this study with use of the photokymograph were essentially identical to those previously described using directly implanted epicardial length gauges,[23,25] endocardial ultrasonic crystals,[1,3,26] contrast angiography[24] and cardiokymography.[12] This recording of the same sequence of morphologic changes over a similar time course after coronary occlusion strongly implies that the fluoroscopic image of epicardial wall motion contains information similar to that recorded by devices that record endocardial (left ventricular angiogram and echocardiogram) or epicardial (length gauges) segmental wall motion (Fig. 7).

Advantages of the technique: Photokymography has associated advantages and disadvantages in comparison with existing techniques. Unlike contrast angiography, it is totally noninvasive and carries only the small risk of the image intensifier fluoroscopic exposure. In contrast to nuclear scintigraphy,[8] videotracking[27] and two dimensional echocardiography,[28] it is simple to perform and is relatively inexpensive because it can be utilized with existing fluoroscopic equipment. Unlike cardiokymography,[12] the analog wave form is not influenced by overlying chest wall motion and can potentially be calibrated.

Limitations of the technique: The technique also has limitations. It requires a high quality stable fluoroscopic imaging system, such as that found in modern cardiac catheterization laboratories. No format yet exists for selecting specific areas of interest, and the range of variability from position to position has not been defined. Assessment of the sensitivity and speci-

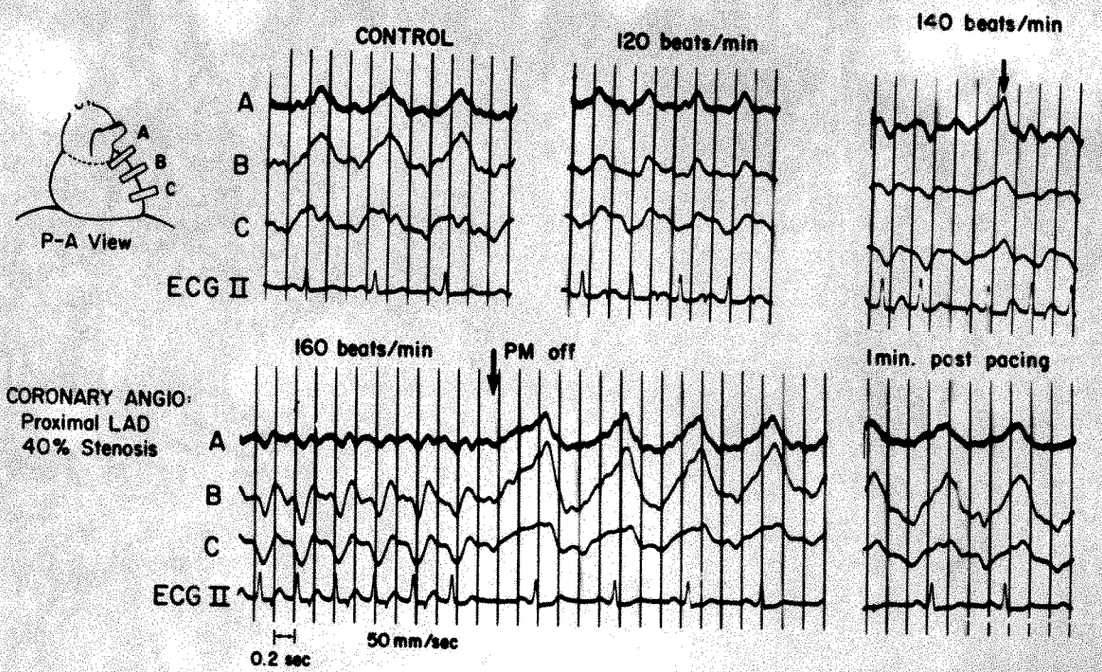


FIGURE 6. Atrial pacing photokymographic study in man. In this patient with an angiographically borderline proximal stenosis of the left anterior descending coronary artery (LAD), fluoroscopic images of the heart were recorded before, during and after 2 minute periods of atrial pacing at increments of 20 beats/min. At each pacing rate, a 3 to 5 second exposure was recorded in the posteroanterior (P-A) projection on video tape at held end expiration. The video tape was replayed, and three photoelectric cells were placed on the cardiac silhouette as indicated by the diagram at **upper left.** The photokymogram was then recorded on a multichannel recorder at 50 mm/sec with 0.2 second time lines along with lead II of the electrocardiogram (ECG) (A = high anterior wall; B = mid anterior wall; C = low anterior wall). In the control period, the predominant motion after the QRS complex is inward (downward) at each location. Relative systolic inward motion is visibly reduced at location C at a pacing rate of 120/min, and at all locations at rates of 140 and 160/min. A miscapture of the pacemaker is noted at a pacing rate of 140/min. Note the improvement in systolic inward motion during the beat closing this longer R-R interval (**arrow**). At the **second arrow** (labeled PM off), the pacemaker is turned off. Note the prompt return of systolic inward motion. Compare the similarity of these wave forms to those in Figure 7. ANGIO. = angiogram.

ficity of the method must therefore await more widespread clinical application. However, in our limited experience the reproducibility and variability of the method do not differ substantially from those associated with subjective analysis of other noninvasive analog techniques such as cardiokymography.[12,13] Placement of the transducer, although not critical, requires knowledge of the spectrum of ischemic and normal patterns of regional wall motion.

Like all noninvasive cardiac imaging techniques, photokymography has the drawback that the complex three dimensional spatial movement of a segment of the

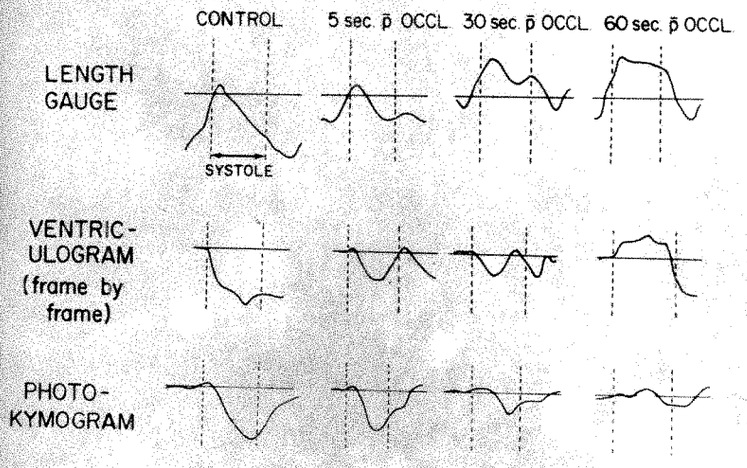


FIGURE 7. Similarity of ischemic segmental wall motion patterns determined with various techniques. **From top to bottom:** epicardial length gauge, segmental frame by frame analysis of the ventriculogram, and photokymogram. Horizontal lines serve as the end-diastolic reference, the vertical lines mark the systolic ejection period. p̄ OCCL. = postocclusion.

heart during contraction or relaxation is compressed into a two dimensional format. The motion of a given segment is the sum of translational and rotational movement of the heart during the cardiac cycle, as well as geometric changes in segment curvature, superimposed on the contraction and relaxation of the segment.[29] Artifactual wave forms due to total cardiac displacement can be reduced by breath holding, but this is difficult to perform immediately after exercise. These shortcomings apply not only to the roentgenkymograph, electrokymograph and photokymograph, but also to computer-based ventricular outline systems. Brower and Messter[30] showed that such distortions are limited to only approximately 5° of arc and that systems that refer wall motion to the centroid of the ventricle tend to minimize these effects. This format is applicable to photokymography and is currently under development.

A second potential limitation of the photokymograph is that only epicardial wall motion is recorded. It has been suggested[31] that epicardial wall motion is less sensitive than endocardial wall motion as a marker of ischemia, although some recent studies[29,32] suggested that if this potential difference occurs, it is too small to be detected. The data in our study, although not directly relevant to this question, also suggest that epicardial wall motion is a comparably sensitive indicator of regional myocardial ischemia, because the time sequence of reduction in inward systolic motion is closely parallel with that previously described using endocardial measurements of segmental wall motion.[24,26]

Implications: Fluoroscopic evaluation of cardiac movement using the photokymograph provides a signal representing segmental wall motion that closely resembles that obtained using established techniques. The device has the advantage of being noninvasive and of relatively low cost, and it provides a beat to beat recording that can be evaluated with serial increments in stress and can therefore be more accurately analyzed than by visual inspection of the real time image alone,[31] especially at higher heart rates. It thus holds promise as a method of clinical evaluation of suspected ischemic heart disease.

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What does this long distance runner have in common



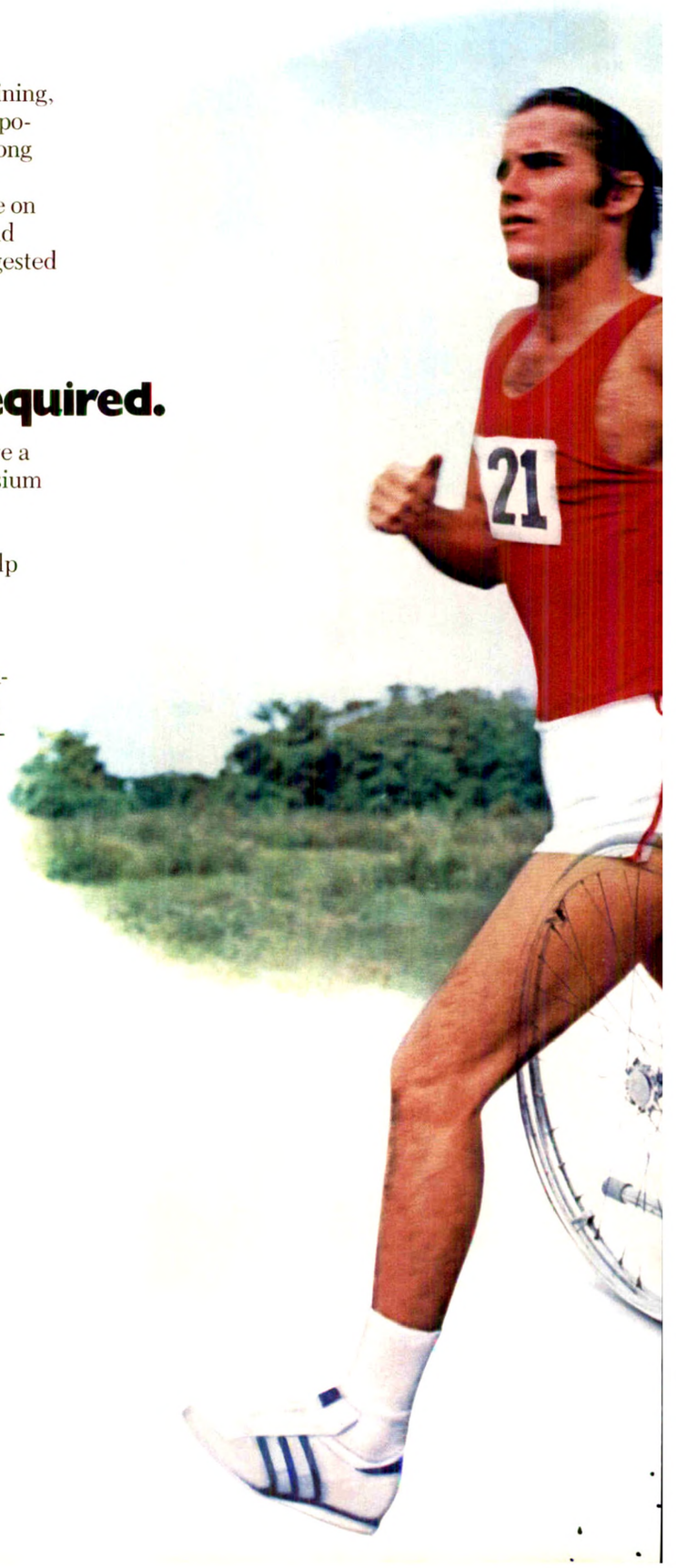
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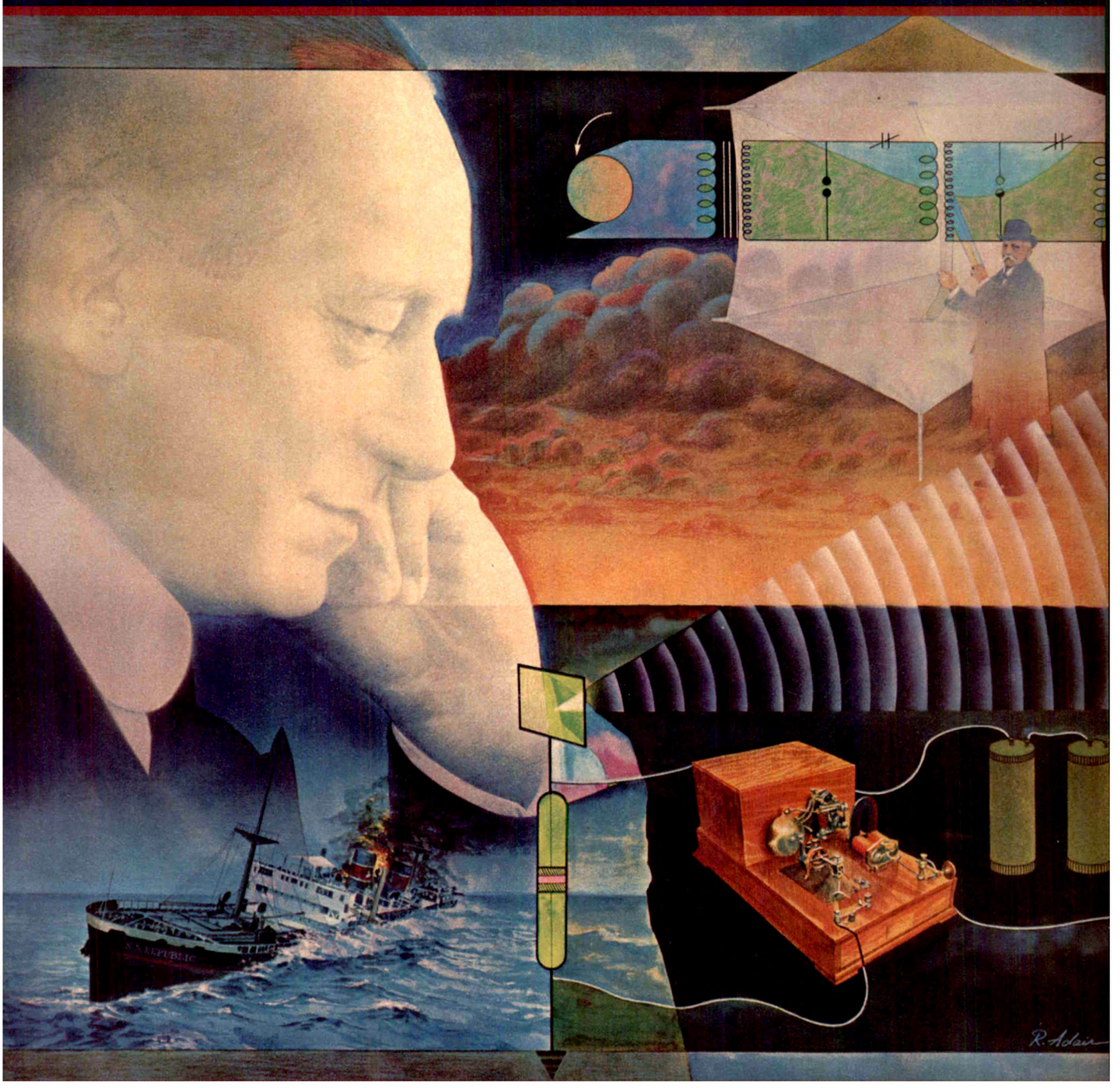
References: 1. Knochel JP, Dotin LN, Hamburger RJ: Pathophysiology of intense physical conditioning in a hot climate. I. Mechanisms of potassium depletion. *J Clin Invest* 51:242-255, 1972. 2. Knochel JP: Exertional rhabdomyolysis. *N Eng J Med* 287:927-929, 1972. 3. Rose KD: Warning for millions: intense exercise can deplete potassium. *Phys and Sportsmed* 3:67-70, 1975. 4. Westerman RL, Snively WD, Jr: Potassium deficit: clinical aspects. *GP* 33:85-93, 1966. 5. Katsikas JL, Goldsmith C Disorders of potassium metabolism. *Med Clin North Am* 55:503-512, 1971.

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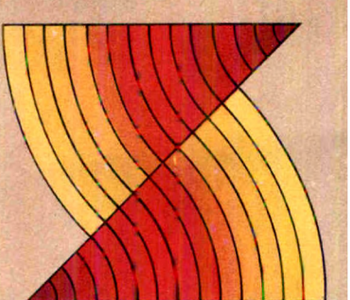
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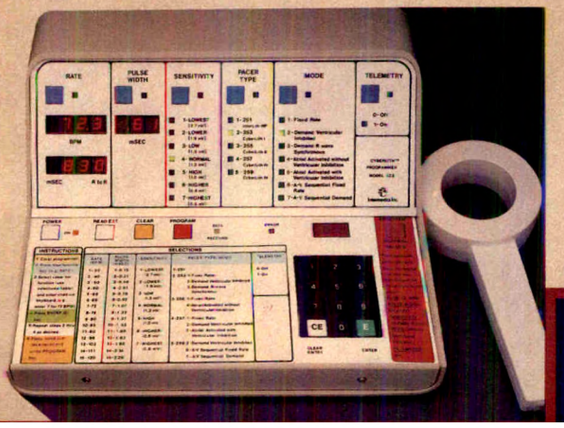
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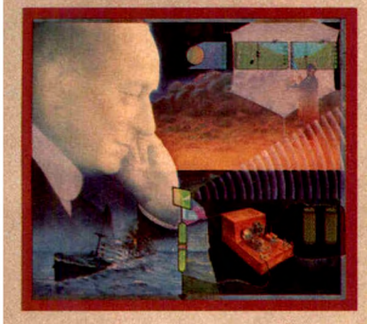
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A battery powered (rechargeable) portable Programmer gives you the flexibility to alter the CyberLith's programmable features individually or simultaneously. In



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Please contact your Intermedics representative for more complete information on the many advantages of CyberLith therapeutic pacing. At Intermedics, we are producing tomorrow's technology today, because OUR BUSINESS IS LIFE.



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The Guglielmo Marconi original water color shown on the first page of this ad is the second in a series commissioned by Intermedics. A limited-edition print, numbered and signed by artist Ron Adair, is being made available by Intermedics to physicians only. To obtain your print please write to Marketing Administration, Intermedics, Inc., P.O. Box 617, Freeport, Texas 77541.

Note:

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Intermedics Pulse Generators

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

PRECAUTIONS Implanted pacemakers have a finite and relatively widely variable service life as a result of factors such as the initial capacity of the battery and the shelf storage time of the manufactured pacemaker; variations in electrode system resistances, stimulation rate, and the percentage of time the implanted pacemaker is inhibited; and random electronic component failures.

Pacemaker operation can be influenced by electric, magnetic, or electromagnetic energy mimicking normal cardiac activity. In addition, certain environmental sources can couple sufficient energy into a pacemaker system to damage the pulse generator. Specifically, diathermy should not be used on pacemaker patients because of possible total inhibition of the pulse generator; electrocautery can inhibit and/or damage the pacemaker as well as cause burns or possible ventricular fibrillation; defibrillation can damage the pacemaker, and the presence of the pacemaker may cause increased cardiac muscle damage from defibrillation. Microwave ovens that do not exceed federal guidelines for leakage (0.5 mW/cm^2 at 2.5 cm from the appliance) will not affect the pacemaker, but leakage in excess of that amount may cause interference. Certain electrical and gasoline-powered appliances can cause inhibition of an implanted cardiac pacemaker system.

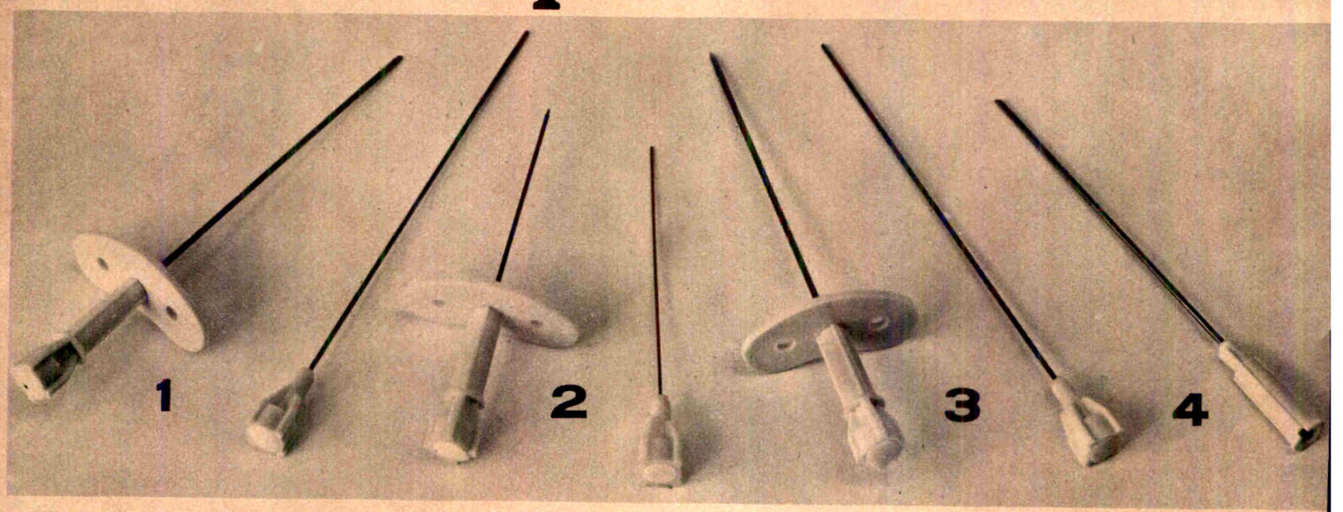
For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

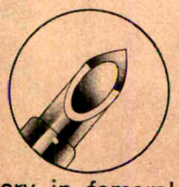
CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

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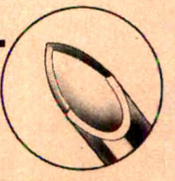
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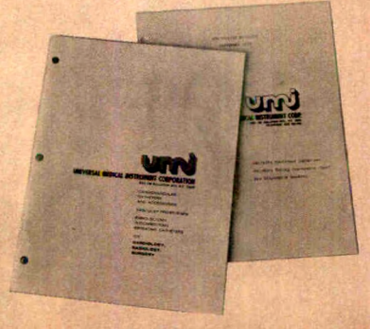
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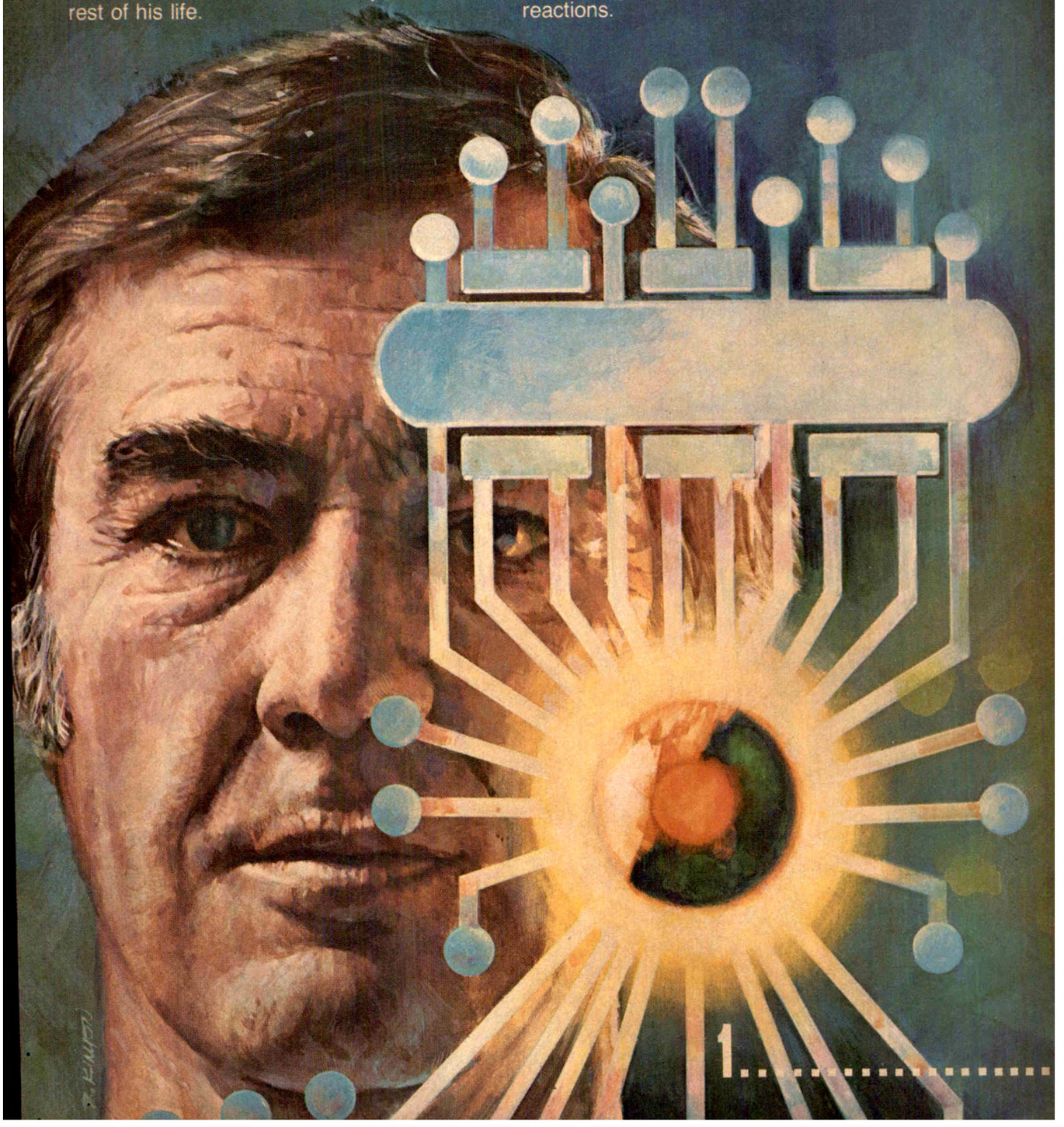
You can improve those odds. Here's how:

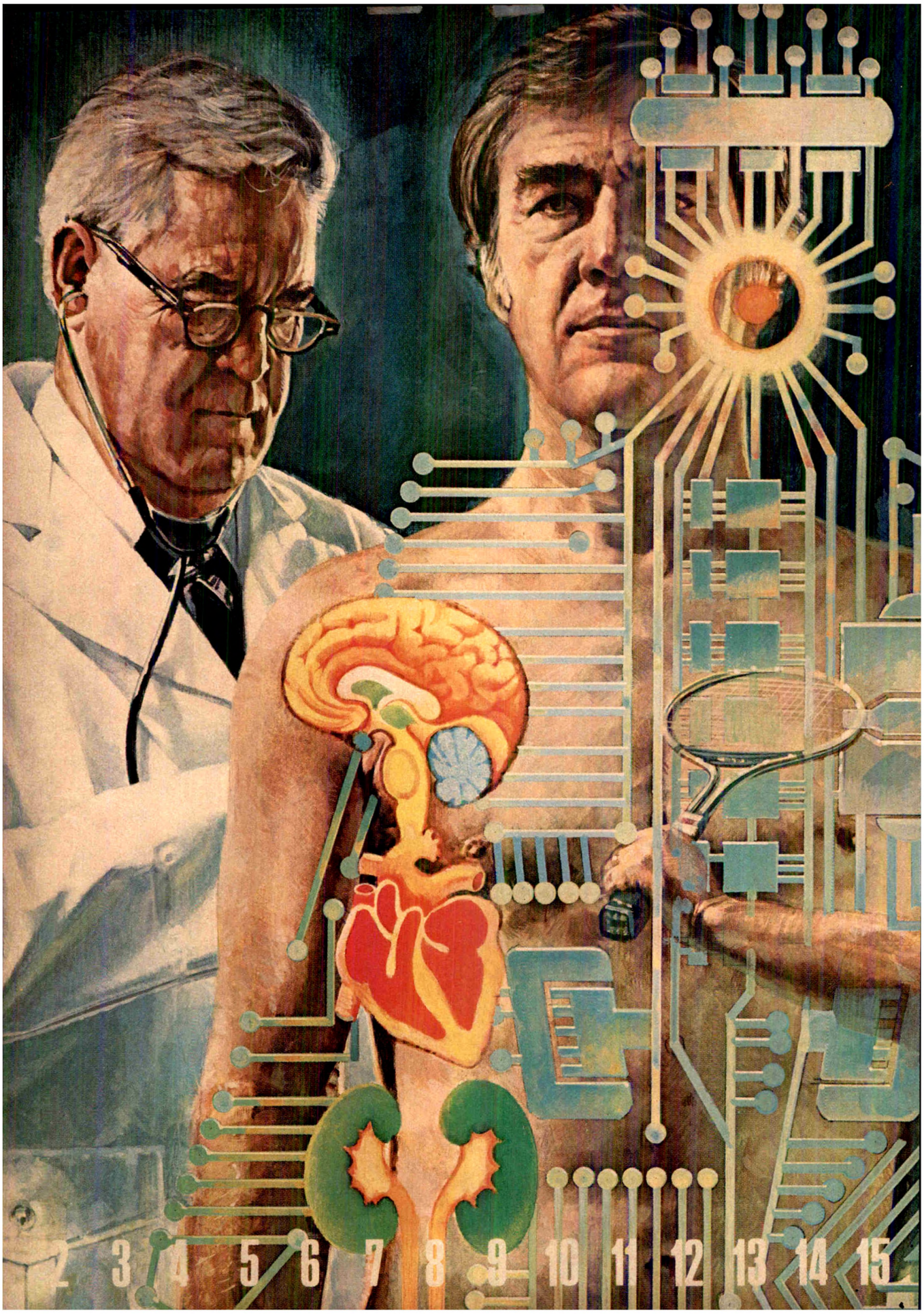
1. COUNSEL: Talk to your patient about the disease and its consequences—about strokes, heart attacks, and kidney failure. Tell him he *must* take medication daily, and for the rest of his life.

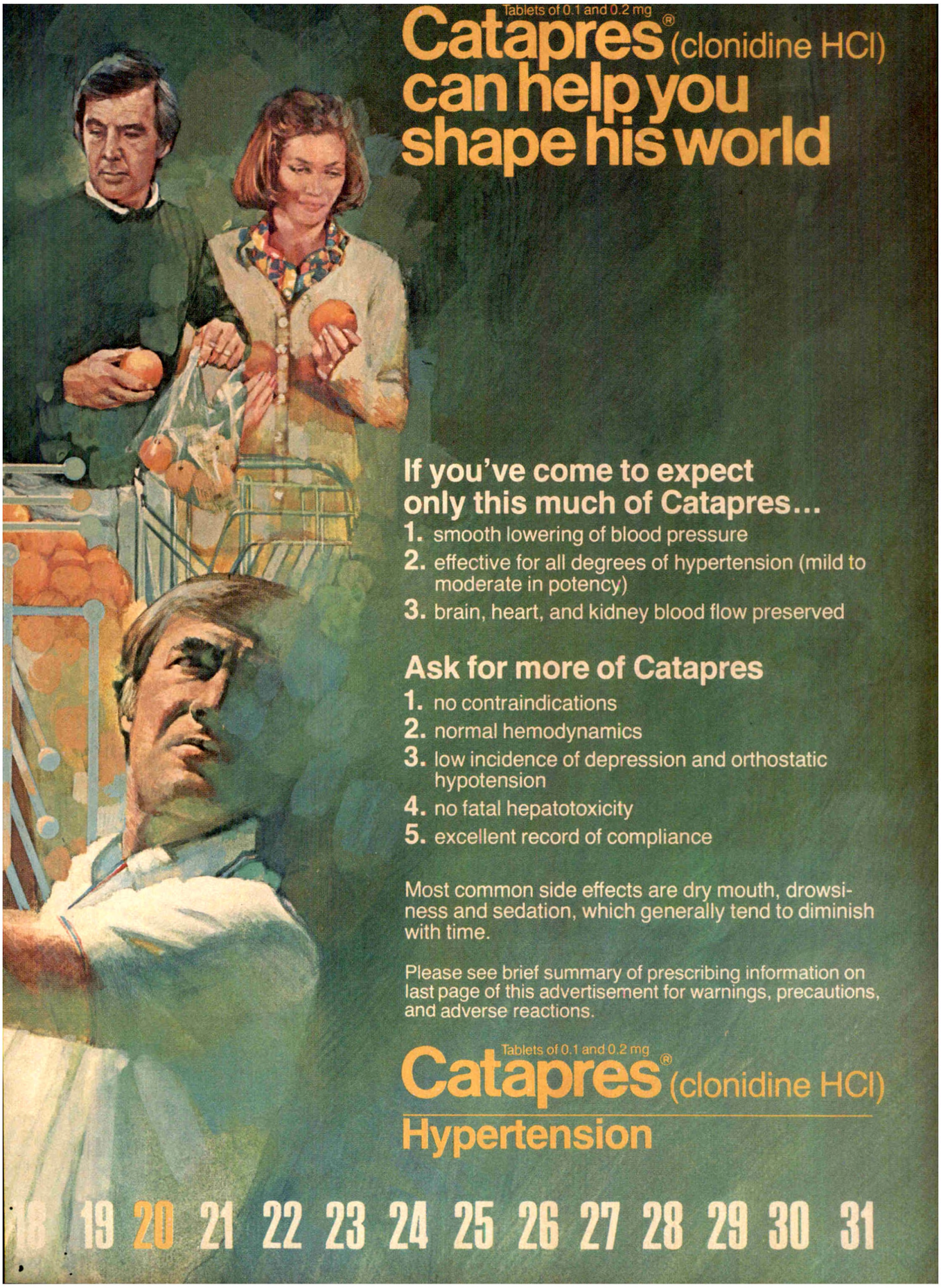
2. CATAPRES® (clonidine hydrochloride): because it works, and people stay with it.[2]

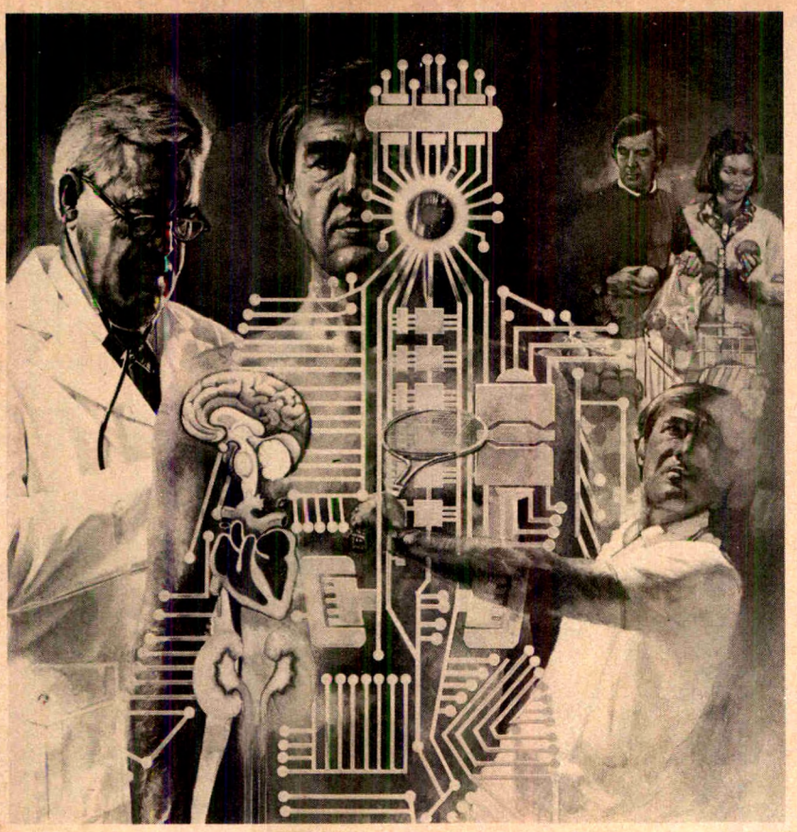
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Tablets of 0.1 and 0.2 mg
Catapres® (clonidine HCl)
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If you've come to expect
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Tablets of 0.1 and 0.2 mg
Catapres® (clonidine HCl)
Hypertension
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Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl) can help you shape his world

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References:
1. Wilber JA, Barrow JS: Am J Med, 52:653-663, 1972.
2. Data on file at Boehringer Ingelheim Ltd.

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Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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Prospective Randomized Trial of Glucose-Insulin-Potassium In Acute Myocardial Infarction

Effects on Myocardial Hemodynamics, Substrates and Rhythm

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PETER H. SEGALL, MD, FACC
HUEY G. McDANIEL, MD
JOHN A. MANTLE, MD, FACC
RICHARD O. RUSSELL, Jr., MD, FACC
CHARLES E. RACKLEY, MD, FACC

Birmingham, Alabama

Fifty consecutive patients admitted within 12 hours of the onset of symptoms of acute myocardial infarction were randomly assigned to treatment with intravenous glucose-insulin-potassium infusion (23 patients) or to a control group (0.5 N sodium chloride infusion) (27 patients). The glucose-insulin-potassium infusion consisted of 30 g glucose, 50 U regular insulin and 80 mEq KCl per liter infused at 1.5 ml/kg per hour for 2 days. Serial measurements were made of pulmonary arterial end-diastolic pressure, cardiac index, daily fluid intake and output, serum glucose, potassium, urea nitrogen, free fatty acids, osmolarity, creatine kinase-MB isoenzyme and cardiac rhythm. Although all patients admitted comatose died (three glucose-insulin-potassium recipients, one control subject), hospital mortality in patients admitted noncomatose was 0 percent (0 of 20) in glucose-insulin-potassium recipients versus 12 percent (3 of 26) in the control group (three deaths secondary to late pump failure). Glucose-insulin-potassium recipients experienced 4.9 ± 1.3 hours of three or more premature ventricular complexes/min compared with 11.1 ± 1.9 hours for control subjects ($P < 0.02$). Twelve control patients had 60 episodes of ventricular tachycardia compared with seven glucose-insulin-potassium recipients, who had 12 episodes of ventricular tachycardia. During glucose-insulin-potassium infusion, fluid intake and output, serum glucose and potassium were significantly increased compared with values in control subjects, blood urea nitrogen and free fatty acids were decreased, whereas osmolarity, pulmonary arterial end-diastolic pressure and cardiac index did not differ significantly from control values. Creatine kinase-MB infarct size averaged 124 ± 15 IU/liter in glucose-insulin-potassium recipients and 109 ± 14 IU/liter in control subjects (difference not significant).

These data demonstrate that, in patients with acute infarction, glucose-insulin-potassium infusion (1) does not adversely alter hemodynamics, (2) reduces free fatty acids, (3) diminishes frequency of ventricular arrhythmias, but (4) has no demonstrable effect on infarct size as assessed with creatine kinase isoenzyme values. In this ongoing randomized clinical trial, the number of patients studied is too small to permit definite conclusions to be reached regarding the effect of glucose-insulin-potassium infusion on hospital survival.

Solutions of glucose, insulin and potassium have been utilized clinically in an attempt to reduce the morbidity and mortality of acute myocardial infarction. Clinical and experimental studies[1-6] have shown that glucose or glucose-insulin infusions suppress elevated levels of potentially toxic serum free fatty acids. Other studies have suggested that glucose-insulin-potassium infusion might lessen the frequency of ventricular arrhythmias,[7-10] reduce myocardial infarct size[11] and limit the mortality

From the Division of Cardiology, Department of Medicine, and the Veterans Administration Hospital, University of Alabama Medical Center, University Station, Birmingham, Alabama. This research was supported in part by the National Heart, Lung, and Blood Institute (Specialized Center of Research for Ischemic Heart Disease, Contract 5P5OHL17667-04, Program Project Grant HL 11310, and the Clinical Research Unit Grant MO-RROOO-13, General Clinical Research Centers Program, Division of Research Resources) of the National Institutes of Health, Bethesda, Maryland.

Address for reprints: William J. Rogers, MD, Division of Cardiology, Department of Medicine, University of Alabama Medical Center, Birmingham, Alabama 35294.

of acute myocardial infarction.[8,12–14] However, other investigators[15–17] have provided conflicting data on the efficacy of glucose-insulin-potassium infusion, and concern has arisen that the osmotic load of the infusion might unfavorably affect left ventricular filling pressure in patients with acute myocardial infarction.[18]

Thus, the purpose of the present investigation was to determine, in patients with acute myocardial infarction, if glucose-insulin-potassium infusion alters left ventricular filling pressure, serum free fatty acid levels, the incidence of ventricular arrhythmias, myocardial infarct size and hospital mortality. This report describes hemodynamic, enzyme, metabolic and rhythm data obtained in the first 50 patients with acute myocardial infarction entered into an ongoing randomized study of the effects of glucose-insulin-potassium infusion.

Methods

Patient Population

The study group was composed of patients admitted to the coronary care unit at the University of Alabama Medical Center with symptoms of acute myocardial infarction and subsequent rise and fall of creatine kinase MB isoenzyme levels. Patients were excluded from this study if baseline data could not be collected within 12 hours of first symptoms of myocardial infarction. We also excluded (1) patients over age 75 years, (2) patients with insulin-dependent diabetes, and (3) patients with acute oliguria (urinary output less than 20 cc/hour) or evidence of chronic renal failure (blood urea nitrogen more than 30 or creatinine more than 2.0 mg/dl, or both); because prior experience[14] demonstrated that these patients tolerate instrumentation and glucose-insulin-potassium infusion poorly.

Study Design

On admission to the coronary care unit, each patient underwent a routine medical history and physical examination (Fig. 1). After giving written, informed consent, all patients underwent bedside right heart catheterization with insertion of a thermistor Swan-Ganz pulmonary arterial catheter. Baseline measurements of pulmonary arterial end-diastolic pressure and thermodilution cardiac index were then obtained.

Patients were then randomly allocated to a glucose-insulin-potassium or control group. The glucose-insulin-potassium group received a solution of glucose, 300 g, potassium chloride, 80 mEq and regular insulin, 50 units/liter, through the right atrial port of the Swan-Ganz catheter at a rate of 1.5 ml/kg per hour[1,14] for 2 days. The control group received 0.5 N saline solution at a minimal "keep-open" rate (approximately 20 cc/hour) for 2 days. Thereafter both groups of patients were treated identically, receiving 0.5 N saline solution at a "keep-open" rate through the Swan-Ganz catheter for an additional 2 days.

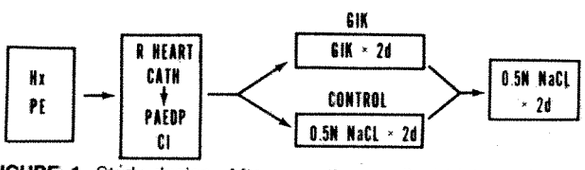


FIGURE 1. Study design. After a routine medical history (Hx) and physical examination (PE), bedside right heart catheterization (r heart cath) was performed, pulmonary arterial end-diastolic pressure (PAEDP) and thermodilution cardiac index (CI) were obtained, and patients were randomly assigned to either a glucose-insulin-potassium (GIK) or a control infusion group.

During the 4 day study period, serial measurements were made of pulmonary arterial end-diastolic pressure, cardiac index, daily fluid intake and output, serum glucose and potassium, blood urea nitrogen, free fatty acids and osmolarity. Samples for creatine kinase MB isoenzyme analysis were obtained at 3 hour intervals for 96 hours after admission and were utilized for creatine kinase MB isoenzyme estimates of infarct size (see later). Cardiac rhythm was monitored continuously during the 48 hour treatment period both by a technician and by a computer system, and ventricular arrhythmias were quantified as described later. Finally, hospital mortality was assessed.

Ancillary drug therapy: Cardiac drugs of proved efficacy were administered for standard clinical indications; however, no drugs were given prophylactically.

After the original hemodynamic assessment, furosemide, sublingual nitroglycerin or isosorbide dinitrate, or both, was administered to patients whose pulmonary arterial end-diastolic pressure was greater than 24 mm Hg in order to reduce this pressure to 20 to 24 mm Hg.[19] Conversely, patients with pulmonary arterial end-diastolic pressure of less than 20 mm Hg and a cardiac index of less than 2.5 liters/min per m^2 were given low molecular weight dextran for volume expansion until pulmonary arterial end-diastolic pressure increased to 20 to 24 mm Hg or cardiac index was greater than 2.5 liters/min per m^2. Dextran or isosorbide dinitrate was also routinely administered on days 2 and 3 of the study protocol for construction of left ventricular function curves.[20] The results of these function curve studies will be reported separately.

Lidocaine was administered intravenously at a rate of 20 to 50 μg/kg per min to patients having six or more premature ventricular complexes/min, premature ventricular contractions occurring in salvos of two or more, ventricular tachycardia, or ventricular fibrillation. Once the ventricular arrhythmia had been completely suppressed for 3 to 4 hours, the lidocaine infusion rate was rapidly tapered to 0.

Digoxin was administered only for treatment of supraventricular tachycardia with rapid ventricular response. No patient was given hyaluronidase, nitroprusside, corticosteroids or propranolol during the study period.

Assay Techniques

Hemodynamic measurements: Pulmonary arterial pressure and thermodilution cardiac index were determined with use of a previously described computerized patient monitoring system.[21]

Chemical determinations: Processing of serial blood samples for creatine kinase MB extraction and calculation of creatine kinase MB infarct size (or accumulated creatine kinase MB release) were performed exactly as recently described in work from our laboratory.[22] Serum glucose and potassium and blood urea nitrogen were measured using standardized automated techniques on Technicon model 1260 and model AA II auto analyzers. Free fatty acids were analyzed according to the method of Itaya and Ui.[23] Osmolarity was determined by freezing-point depression with an Osmette Precision Osmometer, model no. 2007 (Precision Systems, Sudbury, Massachusetts).

Rhythm analysis: Cardiac rhythm was monitored continuously during the study period by both a trained monitor technician and a computerized electrocardiographic recording

system.[24] The technician mounted in a diary those rhythm strips showing the occurrence of atrial or ventricular arrhythmias, or both, conduction disturbances or other significant electrical events. In addition, regardless of the cardiac rhythm, the technician preserved a 15 second rhythm strip obtained every 4 hours, on the hour. The computerized system recorded all normal and abnormal electrical events. From a random 15 min/hour "window" of computerized data and from the technician's diary, it was established whether three or more premature ventricular complexes/min had occurred during each hour. Each episode of ventricular tachycardia (defined as three or more consecutive ventricular complexes at a rate of 150/min or greater) was tabulated. Ventricular arrhythmias were thus expressed as (1) hours of three or more premature ventricular complexes/min, and (2) episodes of ventricular tachycardia per patient.

Statistics: Continuous data are reported as mean ± standard error of the mean. The nonpaired *t* test and chi-square test were used to assess differences between groups of nonpaired data.

Results

Clinical data: Of the 50 patients, 27 were randomly allocated to the control and 23 to the glucose-insulin-potassium infusion group (Table I). Mean age, sex distribution and incidence of prior myocardial infarction were similar in the two groups. Elapsed time from the first symptom of infarction until randomization was similar and averaged approximately 7 hours in the two groups. Ventricular fibrillation or cardiac arrest, or both, before randomization was documented in 28 percent of the patients (14 of 50). Four patients—one in the control group and three in the glucose-insulin-potassium group—had sustained a prolonged cardiac arrest and were deeply comatose on admission. In both groups, anterior infarcts were most common. Hemodynamics and degree of heart failure on admission were similar as assessed by the Killip classification,[25] pulmonary arterial end-diastolic pressure and cardiac index.

The overall hospital mortality rate for the 50 patients was 14 percent (7 of 50). It was 15 percent (4 of 27) in the control group and 13 percent (3 of 23) in glucose-insulin-potassium group (difference not significant). However, in the glucose-insulin-potassium group, all deaths occurred in patients who had sustained prolonged cerebral hypoxia and had been admitted comatose, had been respirator-dependent and had shown no evidence of neurologic recovery throughout their hospitalization. The four deaths in the control group occurred in one patient who had been admitted comatose and in three patients who had been admitted noncomatose but subsequently died of late cardiac pump failure 9 to 11 days after randomization.

No complications attributable to glucose-insulin-potassium infusion were encountered. In five patients, serum glucose levels rose above 300 mg/100 ml, requiring use of supplemental subcutaneous or intravenous regular insulin.

Hemodynamic data: *Left ventricular filling pressure,* estimated from pulmonary arterial end-diastolic pressure[26] (Fig. 2), was elevated on admission in both the glucose-insulin-potassium and control groups but fell proportionately in both groups during the study period. At no time was pulmonary arterial end-diastolic pressure significantly different in the two groups. The dosage and frequency of administration of diuretic drugs, nitrates and dextran were also similar in the two groups (Table II).

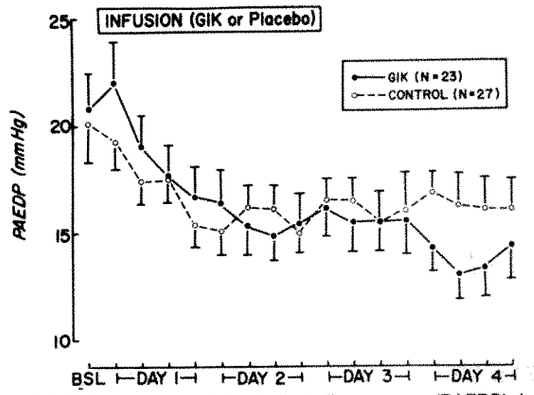


FIGURE 2. Pulmonary arterial end-diastolic pressure (PAEDP) during the study period. The baseline (BSL) pressure was elevated in both the glucose-insulin-potassium (GIK) and the control groups, but decreased proportionately in both groups during the 4 day study period. This variable did not differ significantly in the two groups. N = number of subjects.

Cardiac index averaged 3.0 ± 0.2 liters/min per m^2 during the 48 hour treatment period and 3.6 ± 0.2 liters/min per m^2 during the second 48 hour period in the glucose-insulin-potassium group; the respective values were 3.4 ± 0.2 and 3.8 ± 0.2 liters/min per m^2, in the control group (difference not significant).

TABLE I

Clinical, Hemodynamic and Rhythm Data on Admission*

	Control Group	GIK Group
Patients (no.)	27	23
Age (yr)	58 ± 1	56 ± 2
Sex	24M, 3F	21M, 2F
Prior MI	8 (30%)	11 (48%)
Arrhythmia (before randomization)		
Cardiac arrest/V Fib	5 (19%)	9 (39%)
Atrial fibrillation	3 (11%)	3 (13%)
2° or 3° A-V block	0 (0%)	1 (4%)
Elapsed time until randomization (hr)	6.8 ± 0.3	7.0 ± 0.6
Mental status		
Alert	26 (96%)	20 (87%)
Comatose	1 (4%)	3 (13%)
MI Location by ECG		
Anterior	13 (48%)	13 (57%)
Inferior	8 (30%)	7 (30%)
Undetermined	6 (22%)	3 (13%)
Killip class[25]	1.9 ± 0.2	1.8 ± 0.2
PAEDP†	20 ± 2	21 ± 2
CI†	3.1 ± 0.2	2.9 ± 0.2

* Data in control and glucose-insulin-potassium groups did not differ statistically.

† Hemodynamic variables were measured immediately after Swan-Ganz catheter insertion and before volume manipulation.

A-V = atrioventricular; CI = cardiac index (liters/min per m^2); ECG = electrocardiogram; GIK = glucose-insulin-potassium; MI = myocardial infarction; PAEDP = pulmonary arterial end-diastolic pressure (mm Hg); 2° = second degree; 3° = third degree; V Fib = ventricular fibrillation.

TABLE II
Supplemental Drugs Employed During 48 Hour Treatment Period*

	Control Group (no. = 27)			GIK Group (no. = 23)		
	Recipients (no.)	Dosage/ Recipient	Dosage/ Group	Recipients (no.)	Dosage/ Recipient	Dosage/ Group
Furosemide (mg)	9	111 ± 31	37 ± 14	9	108 ± 47	41 ± 19
Sublingual isosorbide dinitrate (mg)	16	24 ± 2	14 ± 3	18	29 ± 5	23 ± 5
Digoxin (mg)	0	0	0	1	0.5	0.02 ± 0.02
Morphine (mg)	14	14 ± 3	7 ± 2	11	13 ± 4	6 ± 2
Dextran (ml)	10	305 ± 42	113 ± 33	10	284 ± 43	123 ± 35
KCl (mEq)	9	54 ± 12	18 ± 6	5	52 ± 15	11 ± 5

* Distribution of recipients and dosages in control and glucose-insulin-potassium groups did not differ statistically.
GIK = glucose-insulin-potassium; KCl = potassium chloride.

Total fluid intake in the glucose-insulin-potassium group during the 48 hour treatment period averaged 8.5 ± 0.2 liters compared with 4.9 ± 0.3 liters in the control group (P <0.0001). Fluid intake during the second 48 hour period (days 3 to 4) was 4.8 ± 0.2 liters in both groups.

Total measurable fluid output in the glucose-insulin-potassium group was 5.9 ± 0.5 liters during the 48 hour treatment period compared with 4.2 ± 0.3 liters in the control group (P <0.005). Fluid output was similar during the next 48 hours, averaging 3.8 ± 0.3 liters in the control group and 4.0 ± 0.3 liter in glucose-insulin-potassium recipients.

Metabolic data: *Baseline serum free fatty acid levels* were abnormally elevated in both groups on admission (Fig. 3), being slightly higher in the glucose-insulin-potassium group (1113 ± 127 μ mol/liter) than in the control group (782 ± 78 μ mol/liter) (P <0.05). Despite this random baseline disparity, free fatty acid levels fell dramatically in the glucose-insulin-potassium recipients during the 2 day treatment period. Free fatty acid levels fell slowly in the control group, and on days 3 to 4, free fatty acid levels were not statistically different in the two groups.

Serum glucose in the patients treated with glucose-insulin-potassium increased significantly during the 48 hour infusion period (Fig. 4) then fell after discontinuation of the infusion. Glucose levels remained stable in the control patients.

Serum potassium increased significantly during glucose-insulin-potassium infusion and remained greater than control values until about 24 hours after discontinuation of infusion.

Blood urea nitrogen was transiently depressed in glucose-insulin-potassium recipients during the treatment period, also returning to control levels approximately 24 hours after discontinuation of treatment.

Osmolarity was measured twice daily during the 4 day study period and did not differ between glucose-insulin-potassium recipients and control subjects, averaging 279 to 286 mOsm/liter in treated patients and 281 to 287 mOsm/liter in control subjects.

Enzyme data: *Accumulated creatine kinase MB release (creatine kinase MB infarct size)* (Fig. 5) was similar in the two groups, averaging 109 ± 14 IU/liter in control subjects and 124 ± 15 IU/liter in glucose-insulin-potassium recipients (difference not significant). Similarly, expressing creatine kinase MB infarct size as creatine kinase gram equivalents[27] or as IU/liter normalized for body surface area showed no difference between groups. Subdividing the glucose-insulin-potassium and control groups into patients who had been

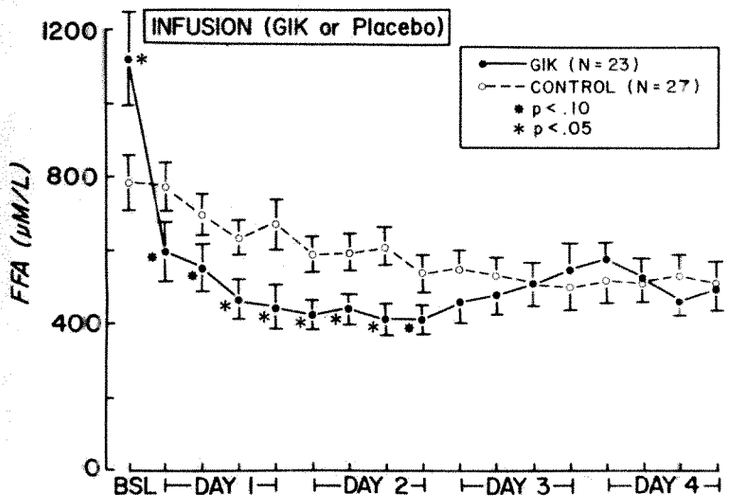


FIGURE 3. Plasma free-fatty acids (FFA) during the study period. Despite a higher baseline (BSL) level, free fatty acids were significantly lower in glucose-insulin-potassium (GIK) recipients than in control subjects throughout the 2-day treatment period. L = liter; M = mol; N = number of subjects; p = probability.

randomized within 6 hours of symptoms and those randomized 6 to 12 hours after symptoms again showed no differences (Fig. 5).

The mean values for the creatine kinase MB disappearance constant, K_d, were similar in glucose-insulin-potassium recipients and control subjects (1.2×10^{-3} min^{-1} in each group). At 12 hours postrandomization, 73 ± 3 percent of total creatine kinase MB release had occurred in the glucose-insulin-potassium recipients, compared with 72 ± 5 percent in the control subjects (difference not significant).

Rhythm data: *The frequency of premature ventricular complexes* decreased during the treatment period in both the control and the glucose-insulin-potassium groups (Fig. 6); however, patients receiving glucose-insulin-potassium had a lesser frequency of premature ventricular complexes during each 12 hour interval of the treatment period. Overall during the treatment period, glucose-insulin-potassium recipients experienced 4.9 ± 1.3 hours of three or more premature ventricular complexes/min compared with 11.1 ± 1.9 hours for control subjects ($P < 0.02$).

Similarly, the frequency of ventricular tachycardia was less in glucose-insulin-potassium recipients than in control subjects (Fig. 7). Twelve control patients had 60 episodes of ventricular tachycardia, whereas seven glucose-insulin-potassium recipients had 12 episodes of ventricular tachycardia.

Lidocaine was administered to patients with ventricular arrhythmias according to the previously described criteria. During most of the treatment period, fewer patients receiving glucose-insulin-potassium required lidocaine, and the total amount of lidocaine employed was less than that in the control group (Fig. 8).

Patients having no detectable periods of three or more premature ventricular complexes/min during the 2 day treatment period tended to have lower mean free fatty acid values during the treatment period (474 ± 42 μmol/liter, no. = 16) than patients who had three or more premature ventricular complexes/min (603 ± 37 μmol/liter, no. = 33) ($P < 0.05$). Mean free fatty acid values were slightly lower in patients having no ventricular tachycardia during the treatment period (531 ± 40 μmol/liter) than in those with ventricular tachycardia (613 ± 38 μ mol/liter), but this difference did not reach statistical significance. Nonparametric (Spearman) correlation coefficient between frequency of

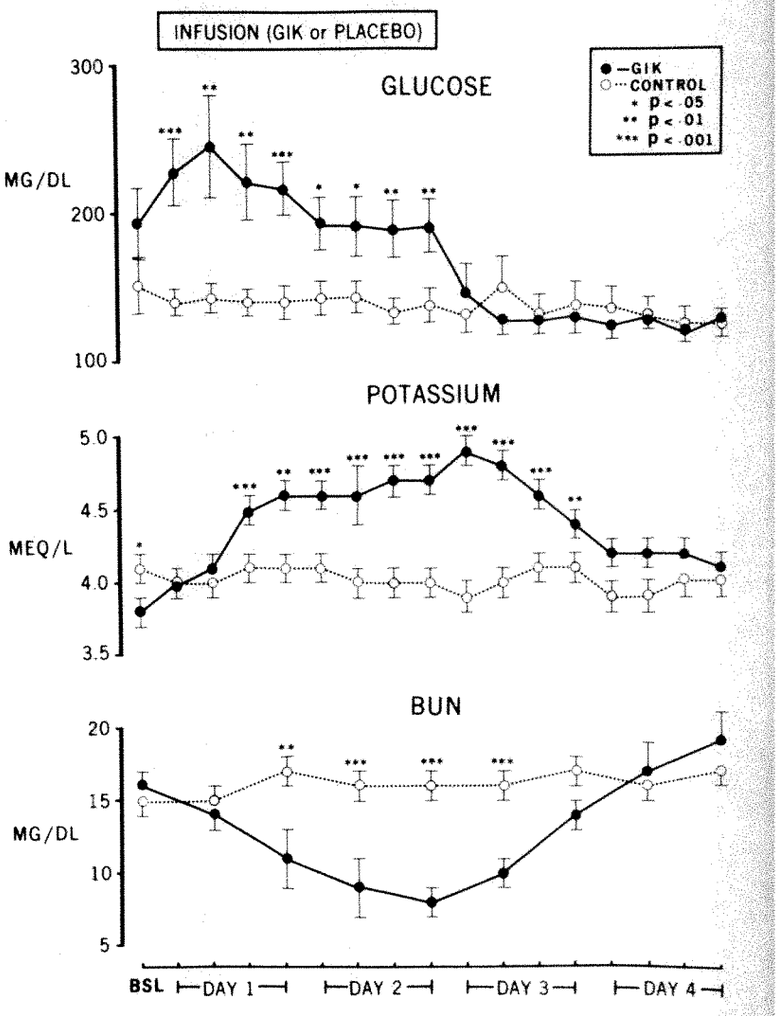


FIGURE 4. Glucose, potassium and blood urea nitrogen (BUN) during the study period. Significant increases in serum glucose and potassium and a significant decrease in blood urea nitrogen were noted in glucose-insulin-potassium (GIK) recipients. BSL = baseline; DL = deciliter; MEQ = milliequivalents; MG = milligram; p = probability.

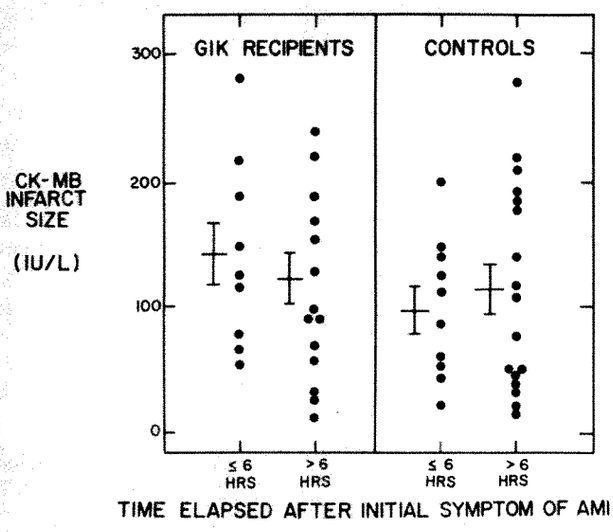


FIGURE 5. Comparison of creatine kinase (CK) MB infarct size between glucose-insulin-potassium (GIK) and control groups. No significant differences in accumulated release of creatine kinase MB isoenzyme were noted, although a wide range of individual infarct sizes was observed. AMI = acute myocardial infarction; L = liter.

premature ventricular complexes and ventricular tachycardia in the 50 patients was 0.62. However, no significant correlations existed between the absolute frequency of ventricular arrhythmias (premature ventricular complexes or ventricular tachycardia) and either free fatty acid levels or infarct size as assessed from creatine kinase MB level.

Discussion

This prospective randomized study demonstrates that glucose-insulin-potassium infusion administered to patients with acute myocardial infarction is associated with a rise of serum glucose and potassium concentrations, a decrease in plasma free fatty acids and a reduction in ventricular arrhythmias but no measurable difference from control values in left ventricular filling pressure, cardiac index, serum osmolarity or enzyme-assessed infarct size. The study population in this ongoing trial is too small at present to permit definite assessment of the effects of glucose-insulin-potassium on hospital survival, although an improved survival in patients admitted to the coronary care unit in a noncomatose condition is suggested.

In a previous nonrandomized study,[14] we suggested that glucose-insulin-potassium infusion might reduce hospital mortality in acute myocardial infarction. The failure of the present study to demonstrate conclusively such reduced mortality may be in part related to the more rigid (randomized) experimental design employed. It is also probably related to the current study's smaller sample size (50 patients versus 134 in the previous study) and lower mortality rates in both glucose-insulin-potassium and control patients—possibly resulting from (1) exclusion of high risk subgroups (elderly, diabetic or azotemic patients), (2) uniform utilization of invasive hemodynamic monitoring, and (3) more liberal use of long-acting nitrates for treatment of postinfarction heart failure.

Hemodynamic sequellae of glucose-insulin-potassium infusion: Because this trial was designed to compare glucose-insulin-potassium-treated patients with "conventionally-treated" control subjects, it was

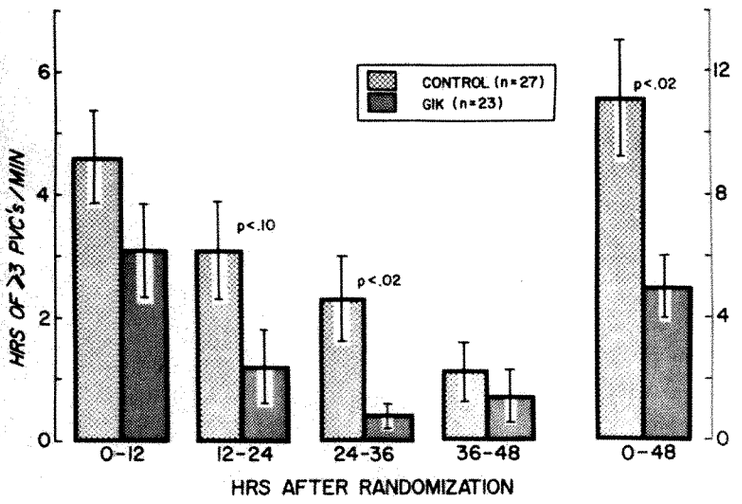


FIGURE 6. Frequency of premature ventricular complexes (PVC's) during the treatment period. During each 12 hour interval after randomization, the incidence of such complexes was less in the 23 glucose-insulin-potassium (GIK) recipients than in the 27 control subjects. n = number of subjects; p = probability.

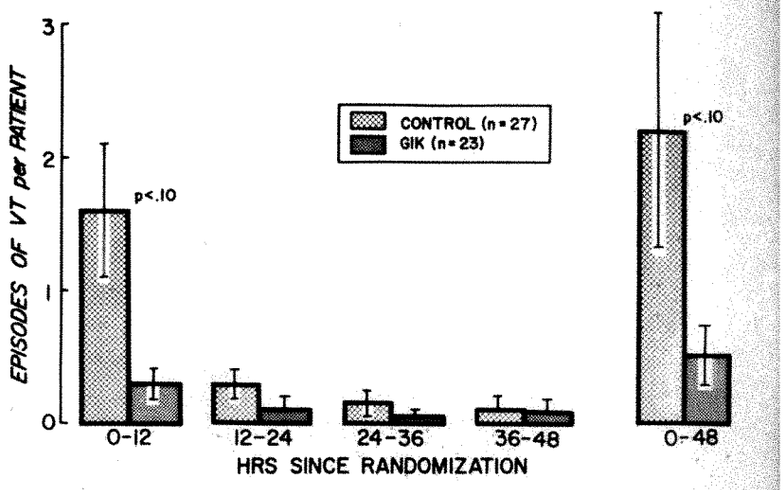


FIGURE 7. Frequency of ventricular tachycardia (VT) during the treatment period. Fewer episodes of ventricular tachycardia were observed in glucose-insulin-potassium (GIK) recipients than in control subjects. n = number of subjects; p = probability.

decided to use as the "control" or placebo infusion a minimal amount of 0.5 N saline solution, a hypotonic, metabolically inert substance. Thus it was not unexpected that fluid intake and output in the glucose-insulin-potassium recipients during the 48 hour treatment period exceeded those of the control subjects. Interestingly, left ventricular filling pressure (pulmonary arterial end-diastolic pressure) remained similar in the two groups, as did cardiac index, serum osmolarity, dosage of nitrates, diuretic drugs, and volume expanders. Thus it was our experience that, with hemodynamic monitoring and adjunctive pharmacologic therapy when needed, glucose-insulin-potassium infusion was well tolerated, even in patients with impaired left ventricular function.

Our experience differs from that of Heng et al.[18] who, using somewhat different methodology, infused a 2 ml/kg bolus dose of 50 percent glucose and then 1.5 ml/kg per hour of 50 percent glucose in patients with acute infarction. These investigators noted a greatly elevated pulmonary arterial end-diastolic pressure 1 hour after the bolus injection, compared with values in control subjects receiving saline solution. However, in our study, no bolus dose of glucose was administered, 30 percent rather than 50 percent glucose maintenance infusion was utilized and serial measurements of pulmonary arterial end-diastolic pressure were made for 96 hours rather than for only 1 hour.

Effect of glucose-insulin-potassium on metabolism: Previous studies from our laboratory[1,2] have demonstrated that glucose-insulin-potassium infusion enhances myocardial carbohydrate utilization while suppressing free fatty acid availability. In the present study, serum glucose was significantly increased and plasma free fatty acid levels were significantly decreased during the study period in the patients receiving glucose-insulin-potassium. Serum potassium levels rose significantly in the glucose-insulin-potassium recipients

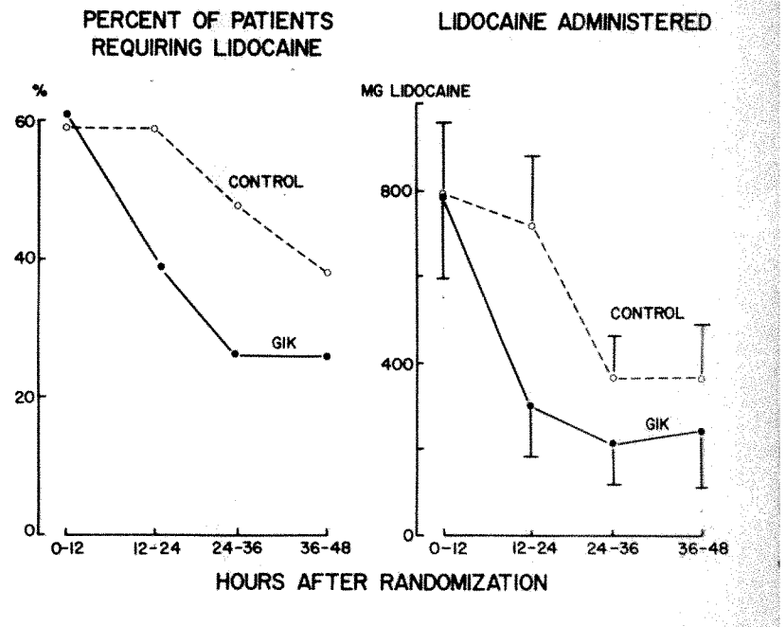


FIGURE 8. Lidocaine usage during the treatment period. During most of the treatment period, fewer glucose-insulin-potassium (GIK) recipients than control subjects were given lidocaine. The dosage of lidocaine administered was significantly ($P < 0.05$) greater in control subjects than in glucose-insulin-potassium recipients 12 to 24 hours after randomization. MG = milligram.

and "peaked" shortly after the abrupt discontinuation of the glucose-insulin-potassium infusion, probably reflecting reflux of intracell potassium into the intravascular compartment. The decrease in blood urea nitrogen during glucose-insulin-potassium infusion was probably related to (1) suppression of hepatic protein metabolism and urea formation secondary to increased carbohydrate availability,[28] or (2) a "dilutional" effect secondary to increased volume of glucose-insulin-potassium infusion compared with control values, or both.

In addition to effects on cardiac metabolism, the potential effects of glucose-insulin-potassium infusion on body nutrition should be noted. The glucose-insulin-potassium infusion supplied approximately 3,000 calories/day to a 70 kg recipient who, in the setting of acute myocardial infarction, might have voluntarily consumed significantly fewer calories as a result of the fatigue, nausea and altered mental status so common after acute infarction.

Glucose-insulin-potassium and myocardial infarct size: Animal studies have demonstrated that infusion of glucose-insulin-potassium after experimental myocardial infarction can reduce myocardial infarct size[11] and preserve tissue glycogen and high energy phosphate stores.[5,6] However, a recent canine study,[29] suggested that glucose-insulin-potassium infusion might delay initial necrosis but exert no long-term effect on reduction of scar size.

The present study in patients with acute infarction demonstrated no difference in accumulated release of cardiac-specific creatine kinase MB isoenzyme between patients treated with glucose-insulin-potassium infusion and control subjects. The rates of creatine kinase MB appearance and disappearance were also similar in the two groups. It should be noted that both glucose-insulin-potassium and control groups showed a wide range of creatine kinase-MB infarct sizes, averaging 115 ± 73 IU/liter (mean ± standard deviation).

Statistical analysis[30] shows that, given this variability in infarct size, a total of about 300 patients in a randomized study would be required to show a 30 percent difference in creatine kinase MB-assessed infarct size between treated and control groups. Furthermore, in the present study of only 50 randomized patients, a difference of creatine kinase MB-assessed infarct size of greater than 70 percent between the two groups might have been missed.

Thus, although a difference in creatine kinase MB-assessed infarct size between the glucose-insulin-potassium and control groups is not demonstrated in our data, the sample size is too small and the individual variability in infarct size is too great to enable us to state definitively that some difference in infarct size between the two groups may not exist. In the future, techniques such as enzyme prediction of infarct size,[31] precordial R wave mapping[32] or serial radionuclide angiography[33,34] may prove more fruitful in assessing effects of glucose-insulin-potassium on infarct size in small patient groups, because these techniques use each patient as his own control.

Suppression of ventricular arrhythmias in glucose-insulin-potassium recipients: Our study demonstrates a reduction in premature ventricular complexes and ventricular tachycardia in glucose-insulin-potassium recipients compared with control subjects, despite use of lesser quantities of intravenous lidocaine in the former group. The precise mechanism for suppression of ventricular arrhythmias in the glucose-insulin-potassium group is not delineated, but several hypotheses are worthy of consideration:

1. *Glucose-insulin-potassium infusion may diminish the automaticity of Purkinje fibers* by repletion of intracell potassium stores lost by ischemic tissue.[7,10,35] Although intracell potassium could obviously not be measured in the present study, serum potassium was observed to rise promptly and significantly in glucose-insulin-potassium recipients compared with control subjects (Fig. 4).

2. *Glucose-insulin-potassium infusion leads to suppression of elevated plasma free fatty acid levels,* which may be arrhythmogenic.[4,36–38] Free fatty acid levels fell significantly in glucose-insulin-potassium recipients and were significantly lower in patients having insignificant numbers of premature ventricular complexes during the treatment period compared with those having three or more premature ventricular complexes/min.

3. *Glucose-insulin-potassium infusion might limit infarct size,* thereby reducing the mass of arrhythmogenic ischemic tissue. However, as previously noted, our data confirm neither a reduction in infarct size in glucose-insulin-potassium recipients nor an overall relation between frequency of ventricular arrhythmias and creatine kinase MB-assessed infarct size.

The beneficial electrophysiologic properties of glucose-insulin-potassium have been further elucidated by recent canine studies showing that glucose-insulin-potassium increased late diastolic threshold, lengthened refractory period[39] and reduced vulnerability to ventricular fibrillation.[40] These experimental observations and our clinical data suggest that glucose-insulin-potassium may impart true antiarrhythmic protection to certain patients with acute myocardial infarction.

Present clinical status of glucose-insulin-potassium infusion in acute myocardial infarction: Our data demonstrate that, with appropriate hemodynamic monitoring, glucose-insulin-potassium can be routinely infused in certain subgroups of patients with acute myocardial infarction, resulting in elevation of serum glucose and potassium levels, lowering of plasma free fatty acid levels and reduction of ventricular arrhythmias. Salutary effects of glucose-insulin-potassium infusion on infarct size and hospital mortality are not yet proved and will likely require analysis of larger patient series in the future.

Acknowledgment

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Paradox of Improved Exercise but not Resting Hemodynamics With Short-Term Prazosin in Chronic Heart Failure

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In patients with chronic heart failure exercise allows the simultaneous observation of the cardiovascular pathophysiology and the symptoms of these patients. We administered short-term, oral prazosin to 10 patients with severe chronic heart failure. Prazosin increased cardiac output and stroke volume significantly during exercise (both $P < 0.05$) but not at rest (both $P > 0.10$). Prazosin decreased the arteriovenous oxygen difference and left ventricular filling pressure significantly during exercise (both $P < 0.05$) but not at rest (both $P > 0.10$). There was no significant correlation between prazosin-induced changes at rest and during exercise in cardiac output ($r = 0.12$), stroke volume ($r = 0.02$), arteriovenous oxygen difference ($r = 0.33$) or left ventricular filling pressure ($r = 0.43$). Prazosin predominantly affects hemodynamics during exercise because its pharmacologic activity as an alpha-adrenergic blocking agent is most prominent during exercise. The full evaluation of prazosin-induced changes in the hemodynamics of patients with chronic heart failure requires evaluation during exercise.

One reason for evaluating drug therapy during exercise in patients with chronic heart failure is to simulate the physical activities that put stress on the cardiovascular system and cause prominent symptoms in these patients. This was the basis for the few published reports on exercise hemodynamics in heart failure after the administration of digitalis,[1] diuretics,[2] phentolamine,[3] nitrates[4,5] and hydralazine.[6] However, if a drug's effects were predictable enough that changes in hemodynamic variables during exercise could be inferred from changes at rest, then it only would be necessary to evaluate the drug at rest because the determinants of the hemodynamic variables would interact with the drug in the same way at rest and during exercise.

In recent years, vasodilator drugs were proposed and evaluated as pharmacologic agents useful for treating heart failure. Resting hemodynamic evaluation of heart failure patients was reported for intravenous,[7-9] sublingual,[10,11] oral[12,13] and topical vasodilators.[14] It was reported that these drugs improve left ventricular performance by increasing stroke volume at the same or a decreased filling pressure. It was speculated that these drugs might improve the peripheral availability of oxygen because of an increased cardiac output. A new drug, prazosin, was recently proposed as a useful agent for treating chronic heart failure because of its favorable effects on resting hemodynamics.[15,16] We evaluated the prazosin-induced changes in the hemodynamics of patients with chronic heart failure during exercise and correlated these changes with the prazosin-induced changes in hemodynamics at rest.

Methods

Patients: We studied 10 patients with chronic heart failure (9 men and 1 woman) with a median age of 65 years (range 46 to 69) who were symptomatic on minimal physical activity or at rest (New York Heart Association class III

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or IV[17]). The patients were selected from an outpatient population. Despite maximal doses of digitalis and diuretic drugs in these patients, their heart failure symptoms were not adequately controlled. The patients were hospitalized at least 24 hours before the initiation of the protocol and were given their usual doses of digitalis and diuretic drugs for the duration of the study. Before baseline measurements were performed, 8 of 10 patients had been hospitalized with bedrest for more than 72 hours, and 3 of the 10 patients had been hospitalized for more than a week. The cause of heart failure was coronary heart disease in five patients and idiopathic cardiomyopathy in five patients. Despite the differences in resting hemodynamic variables among the patients, the minimal left ventricular filling pressure during exercise was 30 mm Hg.

Variables measured: Hemodynamic measurements were performed with the use of a Swan-Ganz triple lumen catheter. These measurements included thermodilution cardiac output (CO) in triplicate (standard deviation ±10 percent) and right atrial pressure. Left ventricular filling pressure was estimated from the mean pulmonary wedge pressure or, if that measurement was inadequate, from the pulmonary arterial diastolic pressure, with the method remaining constant in each patient. The two latter pressures were equivalent because no patient had pulmonary hypertension or severe mitral regurgitation. Blood pressure was measured from a radial arterial catheter. Heart rate was measured from the electrocardiogram during simultaneous determination of cardiac output.

Systemic vascular resistance (SVR) in dynes sec cm^{-5} was calculated as: $SVR = (\overline{AP} - \overline{RA}/CO) \times 80$, where $\overline{AP}$ and $\overline{RA}$ are the mean arterial and mean right atrial pressures, respectively, determined with electronic damping.

Oxygen saturations were calculated from blood gas analysis[18] (Corning, Medfield, Massachusetts), and spot samples were checked for accuracy in each patient by direct measurement of oxygen content[19] (sample variation ±5 percent).

Arteriovenous oxygen difference ($AV\text{-}O_2$) in ml/100 was calculated as $AV\text{-}O_2 = (A_{sat} - PA_{sat}) \times CC$, where A_{sat} and PA_{sat} are the arterial saturation and mixed venous saturations, respectively, and CC is the oxyhemoglobin carrying capacity calculated from the product of the measured hemoglobin and measured oxygen capacity.

Protocol: Hemodynamic measurements at rest and during exercise were performed a few minutes apart with the patient in the postabsorptive state. First, the measurements were performed while the patients were receiving conventional therapy at rest and during exercise. Then the measurements were repeated after oral prazosin was added to the protocol.

The patients performed supine bicycle exercise on an ergometer at a constant pedaling rate of 40 revolutions/min. The center of the bicycle ergometer crank was 12 cm above table level. The initial work load of 100 kilopond-meters (kpm) was increased 50 kpm every 3 minutes. Progressive exercise was performed to the patient's symptom-limited maximum. The symptoms were exhaustion, breathlessness and, in one patient, angina. The median maximal work load was 250 kpm (range 100 to 300). The median duration of exercise was 13 minutes (range 6 to 18). Patients were asked to achieve the same peak exercise work load and pedaling duration after the administration of oral prazosin as they had achieved while receiving conventional therapy. All patients complied with this request except one patient who stopped at a lower work load. The patient with angina duplicated his previous exercise maximum and had similar anginal discomfort.

Drug treatment using oral prazosin administered every 6 hours was started immediately after measurements on conventional therapy were completed. The median initial dose of 3 mg (range 2 to 5) was increased to a median plateau dose of 8 mg (range 5 to 10). The first five patients received an initial prazosin dose of 2 to 3 mg and a plateau dose of 5 to 7 mg, according to body weight. The last five patients received larger doses, after no adverse hypotensive reactions had been observed in the first five patients. The end point of therapy was three plateau doses of prazosin. The median total dose of prazosin before re-exercise was 43 mg (range 23 to 95), and the median duration of prazosin therapy before re-exercise was 47 hours (range 18 to 92). The patients' resting hemodynamics were monitored during therapy. The patients were exercised 2 to 3 hours after the final dose of oral prazosin.

Data analysis: Each patient was observed under four conditions (at rest and during exercise, with conventional and prazosin therapies). Therefore, appropriate statistical testing required the consideration of replicate measurements. The conditions were compared using an analysis of variance and a multiple comparison test.[20] Cardiac output data were incomplete in one patient and arteriovenous oxygen data were incomplete in another patient; these data were excluded from analysis.

Results

Cardiac output (Fig. 1): At rest, cardiac output was 4.1 ± 1.7 liters/min (mean ± standard deviation) with conventional therapy and 5.1 ± 1.5 liters/min when prazosin was added, but the increase was not statistically significant ($P > 0.1$) because of the variation of responses within the group. During exercise, cardiac output increased from 5.7 ± 2.0 liters/min with conventional therapy to 7.4 ± 2.6 liters/min when prazosin was added; this increase was significant ($P < 0.05$). During prazosin therapy, cardiac output increased during exercise because stroke volume increased, but heart rate did not increase (Fig. 2).

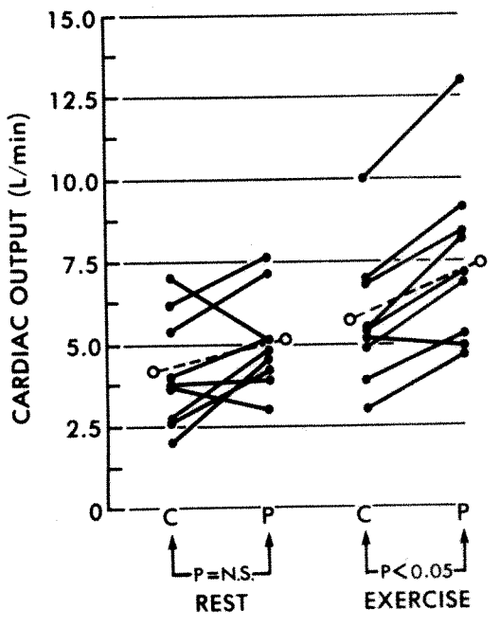


FIGURE 1. Cardiac output. Compared with conventional therapy (C), prazosin (P) increased cardiac output during exercise but not at rest. **Open circles** indicate mean values. L = liters; N.S. = not significant.

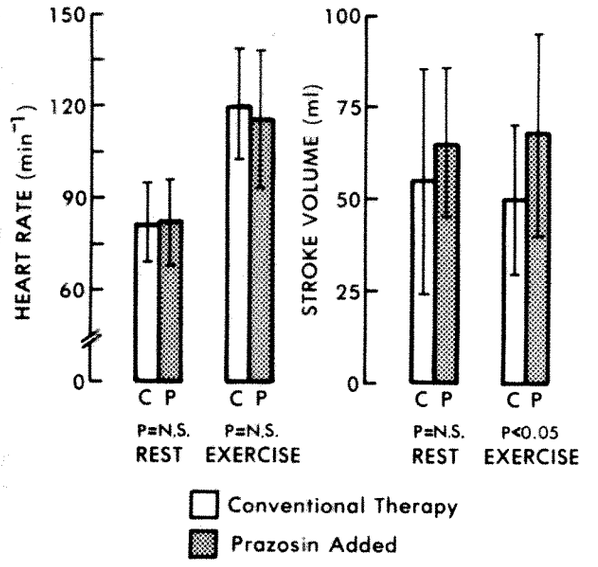


FIGURE 2. Contributions to cardiac output. Compared with conventional therapy (C), prazosin (P) increased stroke volume during exercise but not at rest. Prazosin did not change the heart rate. N.S. = not significant.

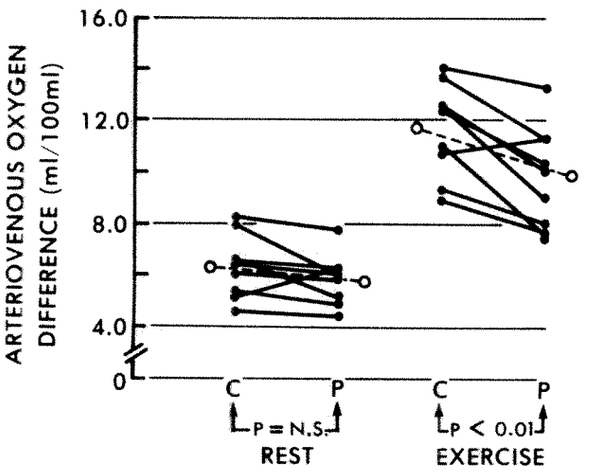


FIGURE 3. Arteriovenous oxygen difference. Compared with conventional therapy (C), prazosin (P) decreased the arteriovenous oxygen difference during exercise but not at rest. **Open circles** indicate mean values. N.S. = not significant.

Arteriovenous oxygen difference and oxygen consumption (Fig. 3): At rest, the arteriovenous oxygen difference was 6.3 ± 1.3 ml/100 ml on conventional therapy and 5.8 ± 1.1 when prazosin was added. However, this decrease was not significant ($P > 0.10$). During exercise, the arteriovenous oxygen difference decreased from 11.7 ± 1.8 ml/100 ml on conventional therapy to 9.8 ± 1.9 when prazosin was added. This decrease was significant ($P < 0.01$). At rest, oxygen consumption (the product of cardiac output and the arteriovenous oxygen difference) was 258 ± 79 ml/min on conventional therapy and 283 ± 87 when prazosin was added. During exercise, oxygen consumption was 641 ± 207 ml/min on conventional therapy, and at the same exercise work load it was 678 ± 209 ml/min when prazosin was added. There was no statistical difference between conventional and prazosin therapy either at rest or on exercise ($P > 0.10$) because the prazosin-induced increases in cardiac output were balanced by decreases in arteriovenous oxygen difference.

Left ventricular filling pressure and intracardiac pressures (Fig. 4): At rest, left ventricular filling pressure was 25 ± 9 mm Hg on conventional therapy and 20 ± 8 mm Hg when prazosin was added. However, this decrease was not significant ($P > 0.10$). During exercise, left ventricular filling pressure was 38 ± 5 mm Hg on conventional therapy and decreased to 30 ± 11 mm Hg when prazosin was added; this decrease was significant ($P < 0.05$). Prazosin also significantly decreased the mean pulmonary arterial pressure on exercise (from 54.5 ± 9.9 to 42.3 ± 12.5 mm Hg, $P < 0.05$) but not at rest (from 34.7 ± 9.8 to 29.3 ± 11.2 mm Hg, $P > 0.10$). Prazosin did not significantly change mean right atrial pressure either on exercise (from 20.9 ± 9.3 to 18.7 ± 9.1 mm Hg, $P > 0.10$) or at rest (from 10.3 ± 5.3 to 9.8 ± 4.7 mm Hg, $P > 0.10$).

Systemic vascular resistance and blood pressure: At rest, systemic vascular resistance was 1,420 ± 455 dynes sec cm^{-5} on conventional therapy and 1,207 ± 409 when prazosin was added. However, this decrease was not significant ($P > 0.10$). During exercise, systemic vascular resistance was 1,125 ± 381 dynes sec cm^{-5} and decreased to 887 ± 368 when prazosin was added. This decrease was significant ($P < 0.05$). Also at rest, mean arterial pressure was 84 ± 12 mm Hg on conventional therapy and 75 ± 6 when prazosin was added ($P > 0.10$). During exercise, mean arterial pressure was 102 ± 14 mm Hg on conventional therapy and 94 ± 16 when prazosin was added ($P > 0.10$).

Comparison of changes in hemodynamic variables (Fig. 5): Prazosin-induced changes in cardiac output, stroke volume, arteriovenous oxygen difference and left ventricular filling pressure at rest were compared with changes on exercise. There was no significant correlation between prazosin-induced changes in cardiac output ($r = 0.12$), stroke volume ($r = 0.02$), arteriovenous oxygen difference ($r = 0.33$) or left ventricular filling pressure ($r = 0.43$) during rest and exercise.

Discussion

Left ventricular performance, already compromised in patients with heart failure, frequently deteriorates further during exercise.[21,22] Decreased left ventricular performance during exercise is, in part, responsible for the pulmonary congestion and decreased exercise tolerance of patients with chronic heart failure. We evaluated left ventricular performance in patients with severe chronic heart failure, both at rest and on exercise and both before and after treatment with oral prazosin. Resting hemodynamics showed that some patients had a normal wedge pressure and some patients had a normal cardiac output. However, during exercise, all patients had a large increase in wedge pressure and an inappropriately small increase in cardiac output. Left ventricular performance while patients were on con-

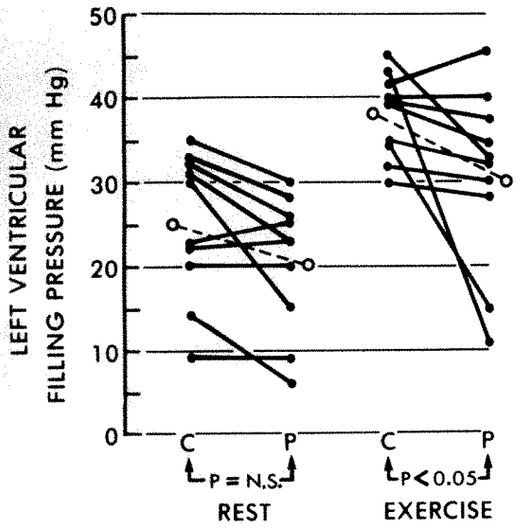


FIGURE 4. Left ventricular filling pressure. Compared with conventional therapy (C), prazosin (P) decreased left ventricular filling pressure during exercise but not at rest. **Open circles** indicate mean values. N.S. = not significant.

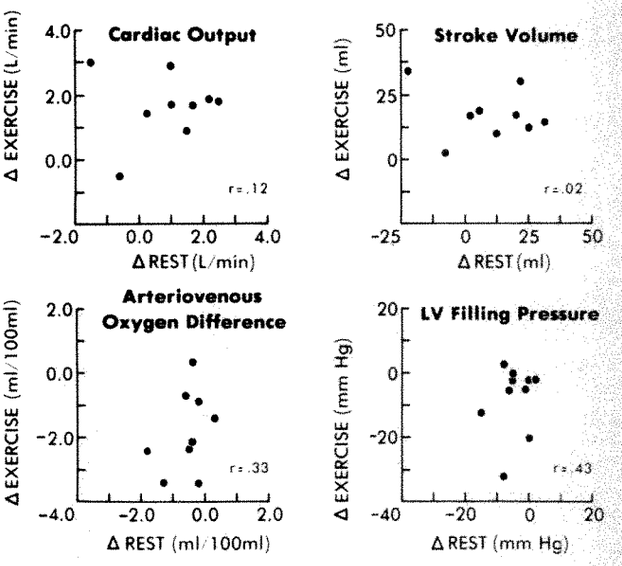


FIGURE 5. Comparison of changes (Δ) at rest and on exercise. Prazosin-induced changes in each of four hemodynamic variables show no significant correlation between values at rest and during exercise. LV = left ventricular.

ventional therapy, as measured by the relation between stroke volume and left ventricular filling pressure, deteriorated from rest to exercise. Left ventricular performance while patients were on prazosin therapy improved at rest and during exercise compared with conventional therapy (Fig. 6). Prazosin improved left ventricular performance more during exercise than at rest because increases in cardiac output and decreases in left ventricular filling pressure were consistently larger during exercise than at rest.

Also, the peripheral utilization of oxygen, as measured by oxygen uptake during exercise, must be considered in evaluating drug therapy for chronic heart failure. Low oxygen uptake during exercise is partly responsible for the fatigue and decreased exercise tolerance of patients with chronic heart failure.[23,24] Oxygen consumption during exercise was the same with conventional and prazosin therapies. Prazosin caused an increase in cardiac output but a decrease in arteriovenous oxygen difference. The net result was no change in oxygen consumption.

Mechanism of prazosin action at rest and during exercise: Both of the results of our study—improved left ventricular performance and unchanged peripheral utilization of oxygen during exercise—can be explained on the basis of prazosin's physiologic mode of action. Pharmacologically, prazosin is a postsynaptic alpha-adrenoreceptor blocking agent.[25] This principal pharmacologic mode of action, recently confirmed in isolated muscle strips[26] and whole animal preparations,[27] might be the major mechanism of its physiologic vasodilating action. Earlier reports also showed that prazosin is pharmacologically active as a direct smooth muscle relaxing agent[28] and as an inhibitor of the smooth muscle enzyme phosphodiesterase.[29] The contribution of these effects to prazosin's physiologic vasodilating activity is unclear. However, prazosin's sympatholytic effect would explain the difference between the hemodynamic changes during rest and exercise.

In humans at rest, a small but variable degree of sympathetic activity contributes to arteriolar tone. On exercise an increase in sympathetic activity increases arteriolar tone in nonexercising portions of the circulation.[30] Consistent with its pharmacologic mechanism of action, prazosin would block sympathetic activity and decrease arteriolar resistance more during exercise than during rest. This action was confirmed by our calculations of decreases in total systemic vascular resistance demonstrating that prazosin decreased resistance more during exercise (21 percent) than during rest (15 percent). The use of resistance as a marker of afterload would also help explain our observations that prazosin increased cardiac output more during exercise than during rest.

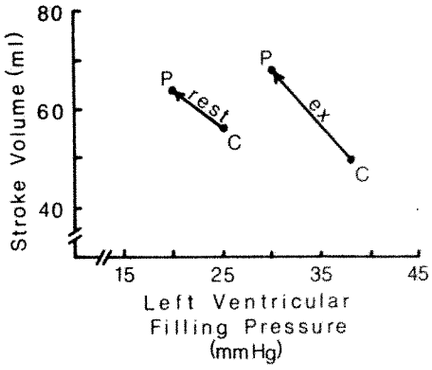


FIGURE 6. Left ventricular performance. Prazosin (P) improved left ventricular performance more than conventional therapy (C) both at rest and on exercise (ex), but the improvement was greater during exercise.

Also, in humans at rest, a small but variable degree of sympathetic activity contributes to venous tone. On exercise, sympathetic tone increases, causing an increase in venous tone in nonexercising portions of the circulation.[31] Consistent with its pharmacologic mechanisms of action, prazosin would block sympathetic tone and decrease venous tone more during exercise than during rest. The use of venous tone as a marker of venous return would help explain our observations that prazosin decreased left ventricular filling pressure more during exercise than during rest.

Because of this mechanism of action, prazosin would improve left ventricular performance more during exercise than during rest but would not improve the peripheral utilization of oxygen. Blocking the increased sympathetic activity of exercise may redistribute the exercise-induced increase in cardiac output. Flow might be shunted through nonexercising portions of the circulation and away from exercising portions of the circulation. Therefore, although total flow increases on exercise, the portion of flow distributed to exercising muscle might be constant or even decreased. This hypothesis is supported by our observations that oxygen consumption was unchanged on exercise despite the increased cardiac output caused by prazosin. However, without measurements of changes in flow or metabolism of regional circulations, the clinical importance of our findings of improved left ventricular performance and unchanged peripheral utilization of oxygen remains conjectural.

Another important finding of this study was that prazosin-induced hemodynamic changes during exercise could not be predicted from changes at rest because prazosin did not cause a comparable change in the magnitude or even direction (in some patients) of hemodynamic variables during rest and exercise. Therefore, whatever changes prazosin causes in left ventricular or peripheral performance must be evaluated with protocols that include measurements during exercise.

Two of the determinants of myocardial oxygen consumption—pulmonary wedge pressure and blood pressure—were reduced by prazosin during exercise. Therefore, it is possible that this effect would increase the exercise work load before the onset of myocardial ischemia in patients with angina pectoris. However, our study was not designed to test this observation because only one patient had angina pectoris.

Differences in results of previous studies: Our observations on the resting hemodynamics of short-term multiple dose prazosin therapy differ from those in reports on the resting hemodynamics of single dose prazosin therapy.[15,16] Prazosin-induced increases in resting cardiac output and decreases in resting left ventricular filling pressure were significant in those reports but were not significant in our study. We previously reported that the hemodynamic effects of the first dose of prazosin are greater and differ significantly from the effects of subsequent doses.[32] The pharmacologic basis of this form of tachyphylaxis is unclear but may account for the differences in the findings in this and previous reports. Other possible reasons for the different findings include different patient populations or protocols. In our study oral prazosin was added to the patient's conventional therapy rather than substituted for conventional therapy. Our study also raises some technical issues related to drug protocols. No dose-response data on the hemodynamic effects of prazosin during exercise are available now. Our preliminary study of resting hemodynamics disclosed no difference between 5 and 10 mg doses.[32] The duration of multiple doses may be important in the development of tachyphylaxis. These questions deserve further inquiry.

Implications: Our study demonstrated that in patients with severe chronic heart failure, the oral administration of prazosin improved left ventricular performance but did not improve the peripheral utilization of oxygen. Our study also demonstrated that hemodynamic changes caused by prazosin during rest were inconsistent and did not predict changes during exercise. Although the precise mechanism of changes in exercise hemodynamics is not known, prazosin might be a useful vasodilator for treating some patients with chronic heart failure—especially patients whose symptoms are most severe during exercise.

Acknowledgment

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Single and Two Dimensional Echocardiographic Features of the Interatrial Septum in Normal Subjects and Patients With an Atrial Septal Defect

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The interatrial septum is one of the least studied structures in M mode echocardiography. Two dimensional echocardiography has made it possible to record simultaneous M mode and two dimensional echocardiograms. Such studies were performed in 10 normal subjects and in 9 patients with a secundum atrial septal defect. In the short axis view of the base of the heart, the interatrial septum was visualized in the two dimensional studies as a linear echo running from the posterior aortic wall to the posterior atrial wall and in the M mode records as a series of dense echoes posterior to the aorta. The great variability in echo dropout of the interatrial septum made it impossible to distinguish the normal subjects from the patients with atrial septal defect. The dense echoes of the interatrial septum in the M mode records gave the false impression that they were filling the left atrium. These data indicate that (1) a secundum atrial septal defect cannot be reliably differentiated from a normal septum using these echocardiographic methods, and (2) the medial location of the interatrial septum should be appreciated so that it will not be confused with a left atrial mass.

The interatrial septum is one of the least studied areas in conventional M mode echocardiography because of the difficulty in recording and recognizing this structure with the M mode technique.[1–4] With the enhanced spatial orientation of echocardiographic anatomy offered by two dimensional ultrasound, it has become easier to image and identify the interatrial septum.[5–7] By combining these two techniques, it is possible to record an M mode echocardiogram of preselected cardiac structures while they are being observed with two dimensional echocardiography. This allows positive identification of a structure before and during its recording with the M mode technique. This method was applied to the interatrial septal echo in order to define further its recognition on M mode echocardiography.

Methods

Ten volunteers with normal findings on cardiovascular examination and nine consecutive patients with a secundum atrial septal defect were examined with a Varian V-3000 ultrasonic sector scanner described previously.[8] Echocardiographic examinations were performed with the patient in the supine or the left lateral position and the transducer in the standard parasternal position.[9] Standard gain settings that allowed all echo-producing structures to be identified without introducing artifacts were used.

Simultaneous M mode recordings were made from any single scan line while the sector scan image was observed.[8] Serial M mode recordings from sequential scan lines across the image field in the area of the interatrial septum were obtained to illustrate the anatomic relations of the interatrial septum as represented on M mode sweeps (Fig. 1). In two of the nine patients with an atrial septal defect,

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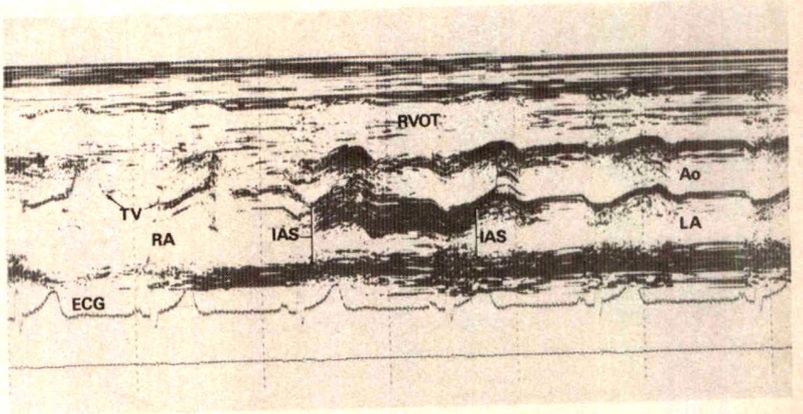


FIGURE 1. M mode echocardiogram taken during the sector scan of a normal subject. The M mode sweep is from the tricuspid valve (TV) and right atrium (RA) to the aortic root (Ao) and left atrium (LA), with the interatrial septum (IAS) appearing between the right and left atria. ECG = electrocardiogram; RVOT = right ventricular outflow tract.

two dimensional echocardiograms were also performed during cardiac catheterization, with the catheter passing through the defect. The plane of the sector scan was aligned with the short axis of the heart at the level of the aortic valve (Fig. 2). With the sector scan transducer in this position, it was possible to visualize the aortic root and valve, the left and right atria, the tricuspid valve and the interatrial septum. Two dimensional echocardiographic photographs in this study were made from the video screen, using a Polaroid® system. The M mode tracings were recorded on a Honeywell recorder that is incorporated into the Varian V-3000.

Results

Normal subjects: The interatrial septum appeared in the two dimensional echocardiogram as a smooth series of echoes extending vertically but slightly medially from the posteromedial boundary of the aortic root (7 o'clock position) to the posterior atrial wall (Fig. 2). There was considerable variability in the echocardiographic appearance of the interatrial septum. On two dimensional echocardiography in 10 normal subjects, the interatrial septum appeared virtually intact in 5 subjects, partially absent in 4 (Fig. 3) and entirely absent in 1 (Fig. 4). In the M mode echocardiogram recorded from the scan lines constituting the two dimensional image, the interatrial septum appeared as either a few or a series of multiple linear echoes posterior to the aortic root (Fig. 1 and 5). The interatrial septum was detected as the scan line producing the M mode was swept from the aorta to the tricuspid valve, and the septum appeared just posterior to the tangentially cut medial portion of the aorta (Fig. 1). In many examples septal echoes appeared to be filling the atrium as the scan line was angled from the left atrium toward the tricuspid valve.

Patients with an atrial septal defect: In the nine patients with a secundum atrial septal defect, echocardiographic discontinuity or absence of the interatrial septum was noted. By ultrasonically imaging the catheter passing from the right atrium to the left atrium during cardiac catheterization, one could localize the area of atrial septal defect to the posterior region of the

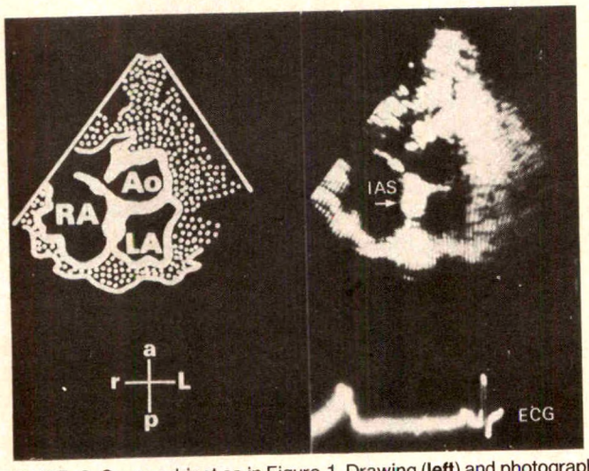


FIGURE 2. Same subject as in Figure 1. Drawing (**left**) and photograph (**right**) of the short axis view at the base of the heart. There is no "echo dropout" of the posterior portion of the interatrial septum (IAS), which extends from the posteromedial wall of the aortic root, angling slightly medial (rightward) toward the posterior atrial wall. a = anterior; Ao = aorta; ECG = electrocardiogram; L = left; LA = left atrium; p = posterior; r = right; RA = right atrium.

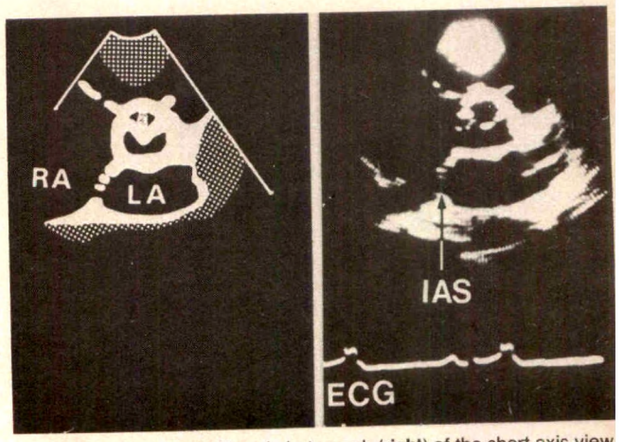


FIGURE 3. Drawing (**left**) and photograph (**right**) of the short axis view at the base of the heart in a normal patient. There is "echo dropout" of the posterior portion of the interatrial septum (IAS) just anterior to its attachment to the posterior atrial wall. Abbreviations as in Figure 2.

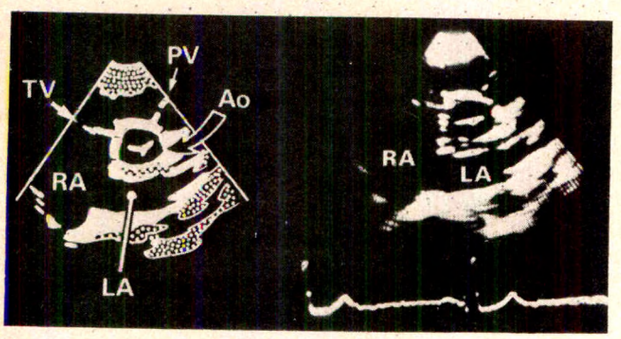


FIGURE 4. Drawing (**left**) and photograph (**right**) of the short axis view at the base of the heart in a normal patient with an echocardiographically absent interatrial septum. PV = pulmonary valve; TV = tricuspid valve; other abbreviations as in Figure 2.

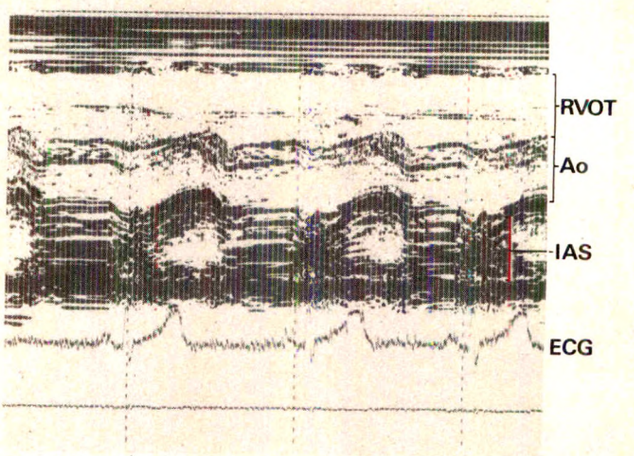


FIGURE 5. Same subject as in Figure 2. M mode echocardiogram of the interatrial septum (IAS) taken from a single scan line during simultaneous two dimensional echocardiography. The interatrial septum (IAS) is represented as a series of linear echoes seen intermittently (predominantly during diastole) posterior to the aortic root (Ao). ECG = electrocardiogram; RVOT = right ventricular outflow tract.

two dimensional image of the interatrial septum. The M mode echocardiogram of the interatrial septum in these patients was very similar to that recorded in normal subjects.

Discussion

Echocardiographic anatomy of the interatrial septum: The combination of two dimensional and M mode echocardiography permits improved anatomic definition of cardiac structures imperfectly appreciated with M mode echocardiography alone. Combining these methods also permits the echocardiographer to understand the effect of cardiac motion that is not parallel with a single scan line resulting in M mode records of a given structure. This effect accounts for the M mode pattern of recording of the interatrial septum (Fig. 1 and 5). In two dimensional echocardiographic pictures of the interatrial septum, this thin structure is represented by a series of vertically stacked linear echoes. Because the interatrial septum is nearly parallel with the M mode ultrasonic beam or individual scan line of a two dimensional system, the septum and beam may interact over a considerable distance within the image field. Individual points on the septum give rise to specific reflected echoes that appear together as multiple lines in these images. These appear as lines rather than points because of the limited lateral resolution of the ultrasonic beam.[10] Such multiple echoes could be confused with masses near the atrial septum. Fortunately, most such masses are mobile and are seen in the area of the mitral valve. However, we know of no sure way using M mode techniques to differentiate echoes from the interatrial septum from a sessile mass attached to the interatrial septum, although recognition of this pattern within the normal interatrial septum should be of assistance.

The variability in the number of echo reflective points along the interatrial septum accounts for the phenomenon of "echo dropout" seen in normal subjects as well as in patients with an atrial septal defect. As noted, this effect is most pronounced when the interatrial septum is aligned parallel with the sampling single ultrasonic beam. Our study of a small number of patients confirms the findings of Dillon et al.[5] and Silverman and Schiller.[6] Work appearing after completion of our study[6,7,11,12] suggests that other transducer locations for two dimensional imaging may place the axis of the interatrial septum more parallel with the ultrasonic beams and increase the visibility and diagnostic utility of visualizing the structure.

Clinical implications: Two dimensional echocardiography has aided understanding of the echoes representing the interatrial septum on M mode echocardiography. The M mode echoes from the interatrial septum do not have a unique motion pattern or character; however, a high expectation that one will encounter them should help to avoid false positive diagnoses of left atrial masses or erroneous identification of these echoes. We believe that our study demonstrates the benefit of combining two dimensional and M mode echocardiography for improved identification of specific echoes recognized in M mode tracings. Physical limitations such as echo dropout are common to both the M mode and the two dimensional technique.

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Right Atrial Ultrastructure in Congenital Heart Disease

II. Atrial Septal Defect: Effects of Volume Overload

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Portions of operatively resected right atrium from 15 patients with atrial septal defect were studied ultrastructurally to determine whether the cell hypertrophy in the right atrium of patients with increased right atrial blood flow and increased right atrial pressure is caused by the increased blood flow. In 12 patients with normal right atrial mean pressure but increased right atrial blood flow the atrium was dilated but no atrial arrhythmias were noted clinically. Ultrastructurally, the atrial myocardial cells in these patients were normal, measuring 6 to 10 μ in diameter, and there was no evidence of cell hypertrophy or degeneration. The remaining three patients had elevated right atrial mean pressure and increased right atrial blood flow. Ultrastructurally, the atrial myocardial cells in all three patients were hypertrophied, and two patients had evidence of focal cell degeneration; the atrium was markedly dilated, but atrial arrhythmias were not noted. The lack of cell hypertrophy in the right atrium of the 12 patients with increased blood flow but normal mean pressure suggests that in congenital heart disease volume overload alone does not lead to cell hypertrophy of the right atrial myocardium.

In a previous report[1] we described changes in the ultrastructure of the dilated right atrium of six patients with endocardial cushion defect. These patients had elevated right atrial mean pressure and increased right atrial blood flow. The ultrastructural changes consisted of cell hypertrophy in all patients and cell degeneration in two patients with markedly elevated right atrial mean pressure. The data suggested that the changes of cell hypertrophy might be secondary to increased blood flow or increased pressure, or both, whereas the degenerative changes appeared to be directly related to increased right atrial pressure. However, we were unable to separate these two hemodynamic values in this group of patients and were thus unable to determine whether increased blood flow or elevated atrial pressure was related to the changes of cell hypertrophy seen in the dilated atrium of these patients with congenital heart disease.

The purpose of this study was to determine whether increased right atrial blood flow in the absence of increased right atrial pressure resulted in hypertrophy of the right atrial myocardium. We studied the ultrastructure of right atrial tissue obtained from patients with atrial septal defect who had a well defined left to right shunt and no evidence of increased right atrial pressure. Although the atrium in these patients was dilated, there was no evidence of cell hypertrophy. Structurally, the atrium was identical to the right atrium of patients with ventricular septal defect[1] and was therefore presumably normal. In addition, portions of the right atrium from three patients with atrial septal defect and increased right atrial mean pressure and blood flow were also studied to determine if the structural changes were the same as those previously reported in patients with endocardial cushion defect.[1] In the patients

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with increased mean pressure and blood flow the right atrial myocardial cells were hypertrophied and there were focal degenerative changes. Our findings suggest that in congenital heart disease increased right atrial blood flow in the absence of increased right atrial mean pressure is not associated with structural changes of the right atrium.

Methods

Patients studied (Table I): Tissue was obtained from 15 patients at the time of open heart surgery for closure of an atrial septal defect. Twelve patients (Group I) had normal right atrial mean pressure (less than 5 mm Hg) and evidence of a left to right shunt across the atrial septum. These patients ranged in age from 8 to 47 years, although 8 of the 12 patients were less than 10 years of age. The atrium was moderately dilated, although the pulmonary arterial pressure was normal (less than 20 mm Hg), and none of these 12 patients had atrial arrhythmias. Three patients (Group II) had elevated right atrial mean pressure (more than 5 mm Hg) as well as a left to right shunt across the atrial septum. These patients ranged in age from 7 to 58 years. The atrium was markedly dilated and the pulmonary arterial pressure was elevated (more than 40 mm Hg) in all three patients; however, they had no atrial arrhythmias.

Tissue preparation: The atrial biopsy specimen was obtained adjacent to the site of the atriotomy on the anterior wall of the right atrium. The tissue was fixed in phosphate buffered (pH 7.3) 2.5 percent glutaraldehyde as previously described.[1] All tissue was fixed overnight in glutaraldehyde, and post-fixed for 1 hour in chilled 1 percent osmium tetroxide in 0.1 molar phosphate buffer (pH 7.3). The tissue was rinsed in phosphate buffer, dehydrated in graded acetones and embedded in Swiss araldite. Flat silicone embedding molds were used to facilitate the orientation of muscle fibers to the endocardium.[2] Thick sections (0.5 to 1 μ) were cut from all tissue blocks in each patient and stained with 1 percent toluidine blue. Ultrathin sections (600 to 800 Å) were cut with a Sorvall MT 2 ultramicrotome, stained with uranyl acetate and lead citrate and examined with a Philips 300 electron microscope at 80 kv.

The incidence of ultrastructural changes in atrial cells of all 15 patients was evaluated. Low power electron micrographs (×3,000) were taken from each grid, and the cells in the thin section counted. At least eight grids and approximately 400 cells were studied in each patient. The cells with ultrastructural changes were counted, and an approximate incidence rate of each ultrastructural change was calculated. The extent of the changes in each patient was then graded on a scale of 1 to 4 (Table II).

Results

Patients With Normal Right Atrial Mean Pressure (Group I, Table II)

Cell size and interstitium: The atrial cells were regularly arranged and relatively uniform in size in each patient. The cells ranged from 6 to 10 μ in diameter at the nuclear level and averaged 8 μ. In well defined pectinate muscles, the atrial cells were aligned parallel to the long axis of the muscle bundles. In the areas where the pectinate muscles merged, the atrial cells were arranged in small bundles, often coursing at right angles to one another. The endocardium measured from 40 to 200 μ in thickness and consisted of collagen fibers, elastic fibers, fibroblasts and smooth muscle cells arranged in a well defined layer beneath the covering endocardial cells. The atrial muscle bundles were surrounded by delicate connective tissue. Scattered normal blood vessels and nerves were present in the interstitium between muscle bundles.

Sarcolemma and specialized junctions: The atrial cells were invested by a basement lamina except at the intercalated discs. The basement lamina was 300 Å thick and consisted of fine filamentous material. This lamina followed the contour

TABLE I

Clinical Data in 15 Patients With Atrial Septal Defect

Case no.	Age (yr) & Sex	Right Atrial Pressure (mm Hg) A Wave	V Wave	Mean	Qp/Qs Ratio	Atrial Size*
Group I (normal right atrial mean pressure)						
1	2F	5	4	3	2.9/1	3+
2	3F	3	2	2	2.2/1	3+
3	3F	7	5	4	2.0/1	3+
4	4F	6	5	4	1.9/1	3+
5	5M	6	6	4	2.0/1	3+
6	6F	6	4	3	1.9/1	3+
7	8M	4	3	2	2.8/1	3+
8	8F	4	3	2	1.8/1	3+
9	11F	6	5	4	1.7/1	3+
10	11M	6	5	3	1.9/1	3+
11	11F	3	3	2	3.0/1	4+
12	47F	—	—	3	5.0/1	4+
Group II (increased right atrial mean pressure)						
13	7F	8	7	7	3.9/1	4+
14	24F	19	28	15	5.0/1	4+
15	58M	10	9	7	5.0/1	4+

* As assessed at the time of surgery: 1+ = near normal size; 2+ = mild dilatation; 3+ = moderate dilatation; 4+ = marked dilatation.

Qp/Qs ratio = ratio of pulmonary blood flow to systemic blood flow.

TABLE II

Structural Changes in 15 Patients With Atrial Septal Defect

Case no.	Average Cell Size (μ)	Z bands*	Intercalated Discs†	Degenerative Changes‡
Group I				
1	6.3	0	+	0
2	8.0	0	0	0
3	5.5	+	0	0
4	7.7	0	0	0
5	7.5	+	0	0
6	7.8	+	+	0
7	7.9	+	+	0
8	8.0	++	+	0
9	8.0	+	0	0
10	7.5	0	0	0
11	7.5	+	+	0
12	7.0	++	+	0
Group II				
13	9.5	+	+++	0
14	11.0	+	++++	++
15	16.0	++	++++	+

* Z band changes include both thickening of Z bands and abnormal accumulations of Z band-like material.

† Intercalated disc changes include increased fibrillar material and irregularity and widening of discs.

‡ Degenerative changes include loss of myofilaments, aggregation of mitochondria and condensation of sarcoplasmic reticulum.

0 = not present; + = present in less than 1 percent of cells; ++ = present in 1 to 5 percent of cells; +++ = present in 5 to 10 percent of cells; ++++ = present in more than 10 percent of cells.

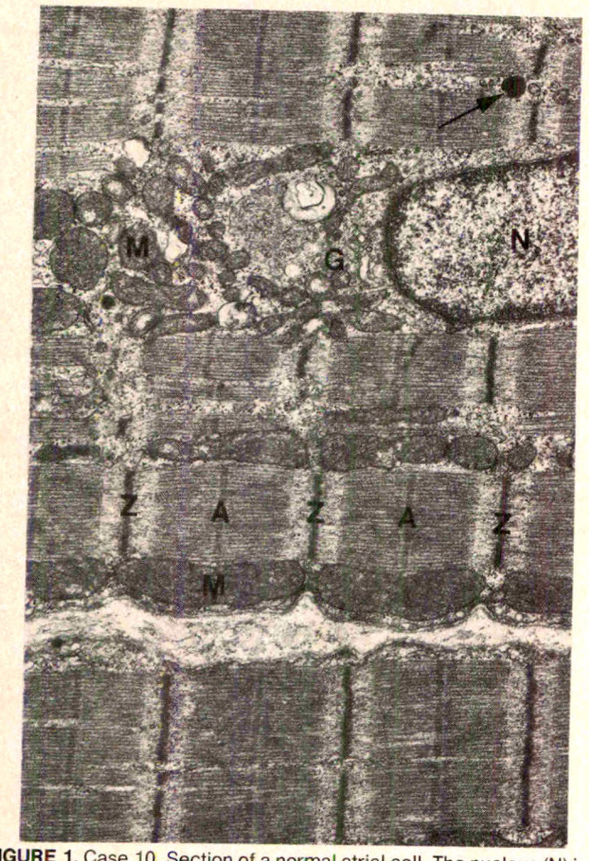


FIGURE 1. Case 10. Section of a normal atrial cell. The nucleus (N) is centrally located and has a regular contour. The myofibrils extend from one end of the cell to the other. The sarcomeres are regularly arranged with distinct A bands (A) and Z bands (Z). Mitochondria (M) are interspersed between myofibrils and are uniform in size. The Golgi apparatus (G) is present in the perinuclear region as are scattered atrial specific granules (**arrow**). The sarcolemma is intact, and T tubular invaginations of the sarcolemma are not seen. (×10,800, reduced by 6 percent.)

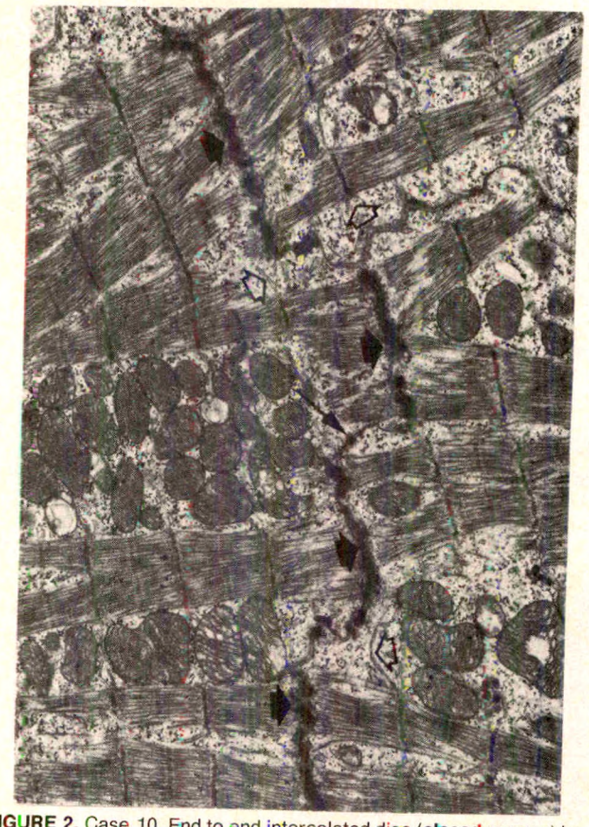


FIGURE 2. Case 10. End to end intercalated disc (**closed arrows**) between two normal atrial cells. The components of this junction are well defined and represent a typical end to end intercalated disc. Nexuses (**thin arrow**) as well as macular adherens, fascia adherens and undifferentiated portions are easily identified, and the disc has a step-like appearance. Segments of the sarcoplasmic reticulum are prominent (**open arrows**) and frequently associated with Z bands. (× 8,100, reduced by 6 percent.)

of the atrial cells but was separated from the sarcolemma by a space 200 to 300 Å in width. The sarcolemma was intact and slightly indented at the level of the Z bands (Fig. 1), except at the intercalated discs. Clusters of pinocytic vesicles were often found beneath the sarcolemma. Deep invaginations of the sarcolemma to form T tubules were not seen in the atrial cells examined. On the interior aspect of the sarcolemma, there were scattered irregular deposits of Z band material (less than 1 percent of cells examined). Occasionally these deposits were continuous with the Z bands of adjacent sarcomeres. The atrial cells were interconnected at their ends by well developed intercalated discs (Fig. 2). At side to side junctions, the intercalated discs were often short and consisted of macula adherens, fascia adherens and unspecialized areas (Fig. 3). Occasionally, extensive side to side intercalated discs were complete with fascia adherens, macula adherens, macula occludens and unspecialized areas. Less than 1 percent of the intercalated discs in 6 of the 12 patients were either irregular in appearance or had extensive accumulations of fibrillar material (Fig. 4).

Contractile elements: The sarcomeres were regularly arranged and extended uninterrupted across the cell. The sarcomeres were limited by Z bands and had distinct A bands, I bands and M lines. The thickening of the Z bands was found in all 8 of the 12 patients but was present in less than 1 percent of the cells examined in all but 2 patients. Occasionally single Z bands were thickened. More often, multiple Z bands (in consecutive sarcomeres) were thickened within a single cell (Fig. 5). These abnormal Z bands consisted of several irregular nodules that were either connected to one another by a normal segment of the Z band or completely separated from one another by glycogen particles. The involved sarcomeres were disorganized with focal loss of myofilaments, but A bands and M lines remained recognizable (Fig. 5).

Cell organelles: The nucleus was centrally placed and elliptical. Only small invaginations of the nuclear membrane were noted (Fig. 1 and 3). Nucleoli were prominent and occasionally multiple. The mitochondria were abundant and most numerous in the perinuclear regions as well as between the myofibrils (Fig. 1 and 3). The mitochondria were round or ovoid, ranging from 0.1 to 0.8 μ in diameter. The cristae were well defined, and the matrix was highly electron-opaque and often contained small dense bodies and glycogen particles. Glycogen was abundant and consisted primarily of beta particles with a diameter of approximately 280 Å. Atrial-specific granules were numerous (Fig. 3). These granules were completely enveloped by a membrane; they measured 0.1 to 0.4 μ in diameter and were most numerous in the perinuclear zones. Lysosomal granules were occasionally found in the perinuclear zones. The Golgi apparatus was well developed

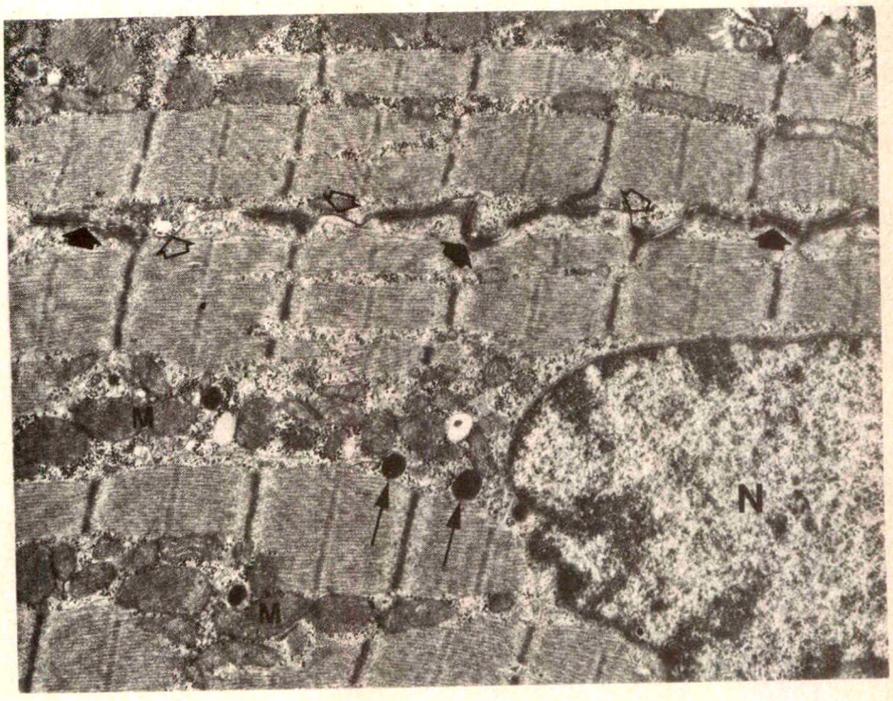


FIGURE 3. Case 10. Two adjacent normal atrial cells joined by a side to side intercalated disc. The disc (**closed arrows**) is regularly arranged and consists of macular adherens, fascia adherens and undifferentiated portions. Macular occludens (nexuses) are present (**open arrows**). **Thin arrows** indicate atrial specific granules. M = mitochondria; N = nucleus. (×14,200, reduced by 6 percent.)

and consisted of stacks of cisternae 150 to 200 Å apart and groups of microvesicles ranging from 400 to 800 Å in diameter. The Golgi apparatus was invariably present in the perinuclear zone in apposition to the nucleus (Fig. 1).

The sarcoplasmic reticulum was extensive and was most conspicuous at the periphery of the cell or in cytoplasmic areas devoid of myofilaments. It was usually seen in profile as vesicles with a diameter of 300 to 800 Å; however, tubules of the sarcoplasmic reticulum were also seen overlying sarcomeres at the level of the Z band (Fig. 2). Tubules of rough sarcoplasmic reticulum were occasionally found near the nuclear membrane or at the periphery of the cell. Small lipid droplets were present adjacent to mitochondria, and lipochrome pigment was occasionally present in the perinuclear region.

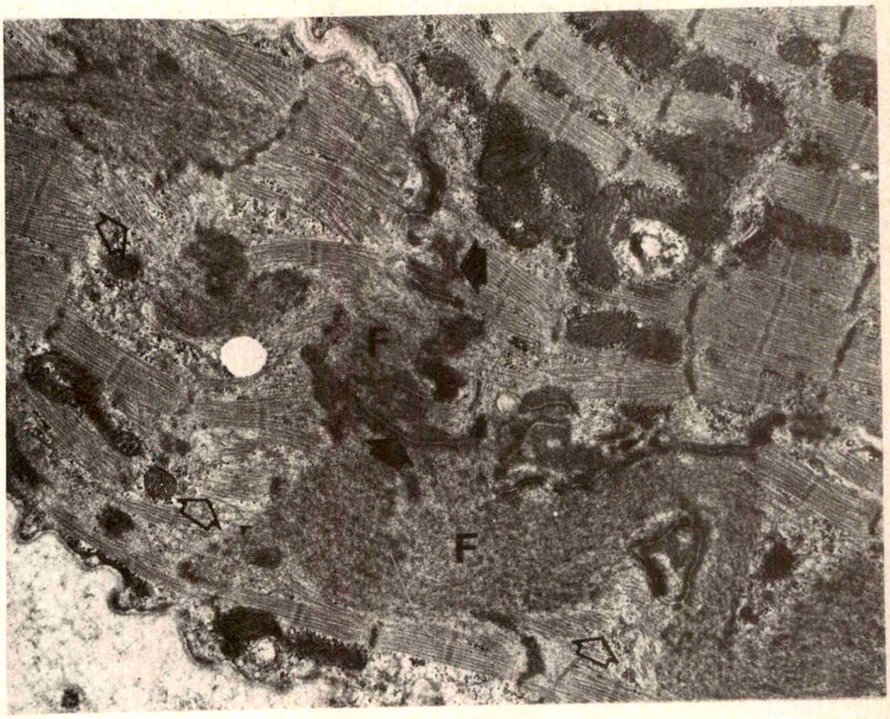


FIGURE 4. Case 8. An irregular, abnormal end to end intercalated disc (**closed arrows**) associated with extensive deposition of fibrillar material (F) between two otherwise normal atrial cells. This disc abnormality was more extensive in patients in Group II. Note the disarray of sarcomeres bordering the fibrillar masses (**open arrows**). (×10,500, reduced by 7 percent.)

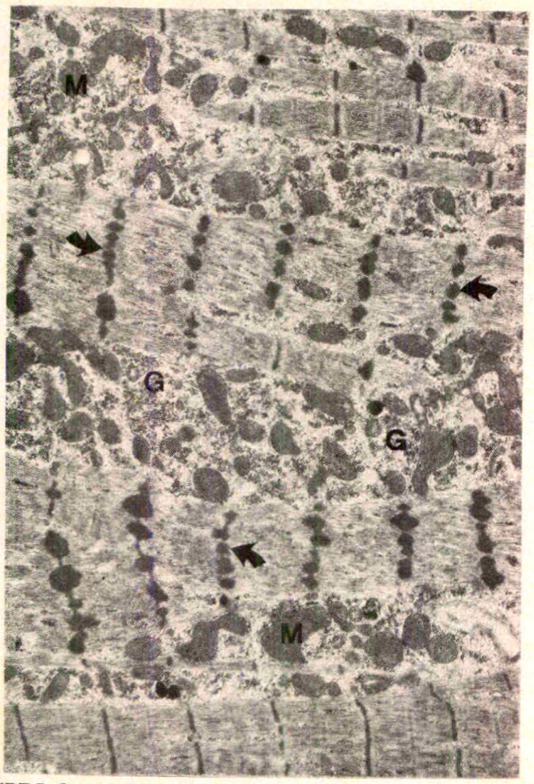


FIGURE 5. Case 8. A small portion of an atrial cell with multiple Z band thickenings (**arrows**). The thickenings are small and nodular and extend along the entire Z band in beaded fashion. The myofilaments in affected sarcomeres are slightly disarrayed, but there is no apparent loss of myofilaments. G = glycogen; M = mitochondira. (×8,100, reduced by 8 percent.)

Patients With Increased Right Atrial Mean Pressure (Group II, Table II)

There were extensive structural changes in the right atrium of these three patients. The cells were generally hypertrophied, although there were focal degenerating cells in Patients 14 and 15. The interstitial connective tissue was increased in amount, and the endocardium was thickened, measuring 300 to 500 μ. Blood vessels and nerves were numerous and appeared normal.

Cell size: The atrial cells varied in size, shape and arrangement. The diameter of the cells at the nuclear level ranged from 7 to 18 μ. There were three distinct populations of myocardial cells: normal cells, hypertrophied nondegenerated cells and degenerating cells. The ultrastructural criteria for hypertrophy and degeneration in human atrial myocardium have previously been published.[1] The normal cells measured 7 to 12 μ in diameter. In Patients 13 and 14 approximately 50 percent of the cells examined were greater than 12 μ in diameter. The most extensive cell hypertrophy was seen in Patient 15. The average cell diameter in this patient was 16 μ, and more than 75 percent of cells examined were greater than 12 μ. The hypertrophied cells bulged slightly at the nuclear level and tapered sharply at both ends. These cells were arranged in bundles of three to five cells, all aligned parallel to one another; however, the muscle bundles were separated from one another by abundant interstitial connective tissue.

Less than 5 percent of the cells examined demonstrated degenerative changes. Cells with early degenerative changes (Fig. 6) were generally hypertrophied and measured 14 to 18 μ in diameter. Cells with severe degenerative changes (Fig. 7, left) were generally smaller and averaged 10 μ in diameter. These cells were isolated from the surrounding atrial myocardium by abundant connective tissue.

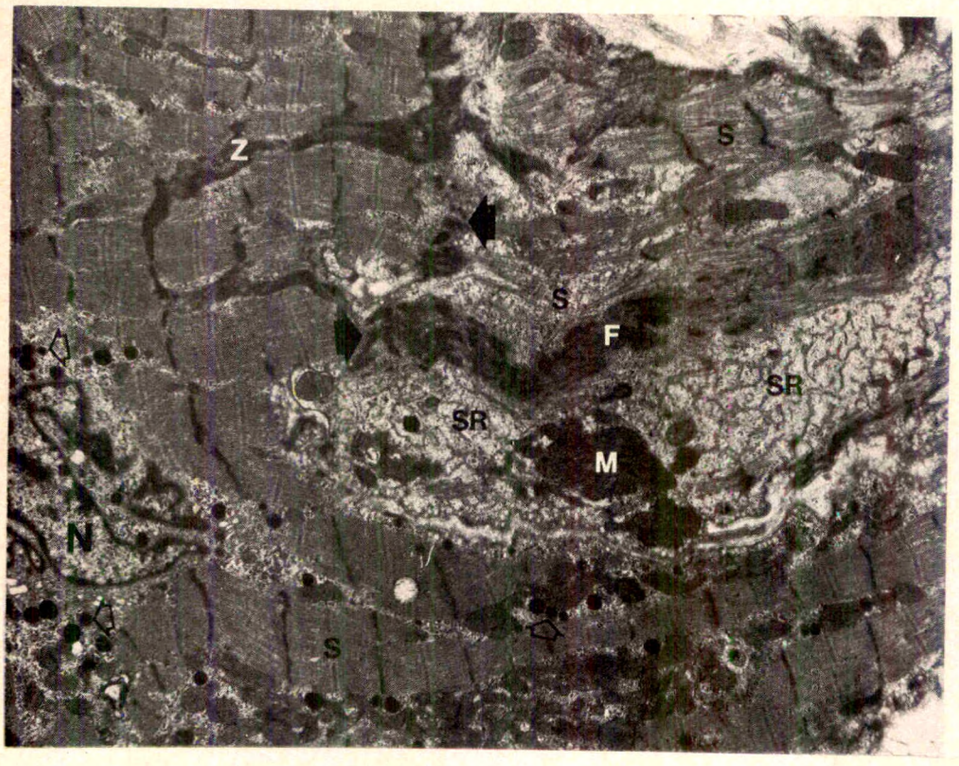


FIGURE 6. Case 15. A portion of an intercalated disc (**closed arrows**) between a hypertrophied cell (**left**) and a cell with early degenerative changes (**right**). The disc is irregular, widened and associated with fibrillar material (F). In the degenerating cell, profiles of sarcoplasmic reticulum (SR) and clumps of mitochondria (M) are evident in areas devoid of myofibrils. The remaining sarcomeres (S) are intact but disarrayed. In the hypertrophied cell the nucleus (N) is markedly convoluted and there are focal thickened Z bands (Z). The sarcomeres (S) are intact and well ordered. Atrial-specific granules (**open arrows**) are numerous. The sarcolemma and basement membrane of both cells are normal. (×8,100, reduced by 8 percent.)

Sarcolemma and specialized junctions: The sarcolemma and basement membrane were normal in both hypertrophied and degenerative cells (Fig. 6 and 7, left). Many of the intercalated discs in hypertrophied cells and cells with early degenerative changes were markedly irregular and had increased amounts of fibrillar material. These disc changes were identical to those described in patients with normal right atrial mean pressure; however, they were present with increased frequency in patients with elevated pressure (10 percent or more of the cells examined). Intercalated discs were not found in severely degenerative cells (Fig. 7, left); however, less than 1 percent of cells examined demonstrated these severe degenerative changes.

Contractile elements: The hypertrophied cells had increased numbers of well formed, well ordered myofilament bundles with distinct sarcomeres. As previously reported,[1] loss of myofilaments was one hallmark of degenerating cells. In severely degenerating cells (Fig. 7, left) only remnants of myofibrils were present at the periphery of the cell. Z band changes similar to those described in patients in Group I were present in all three patients in Group II. Thickened Z bands and accumulations of abnormal Z band material were present in all cells with degenerative changes. In addition, accumulations of Z band material against the sarcolemma were prominent in degenerating cells. Z band changes were also present in hypertrophied cells but were found in less than 5 percent of the cells examined.

Cells organelles: The cell organelles appeared to be increased in number but were normal in hypertrophied cells. In degenerating cells there were aggregates of sarcoplasmic reticulum tubules, glycogen and mitochondria in areas of myofilament loss (Fig. 6 and 7). The mitochondria were small and irregular with dense matrixes and occasionally vacuolated. Atrial-specific granules were present in both hypertrophied and degenerating cells.

Approximately 10 percent of the degenerating cells in Pa-



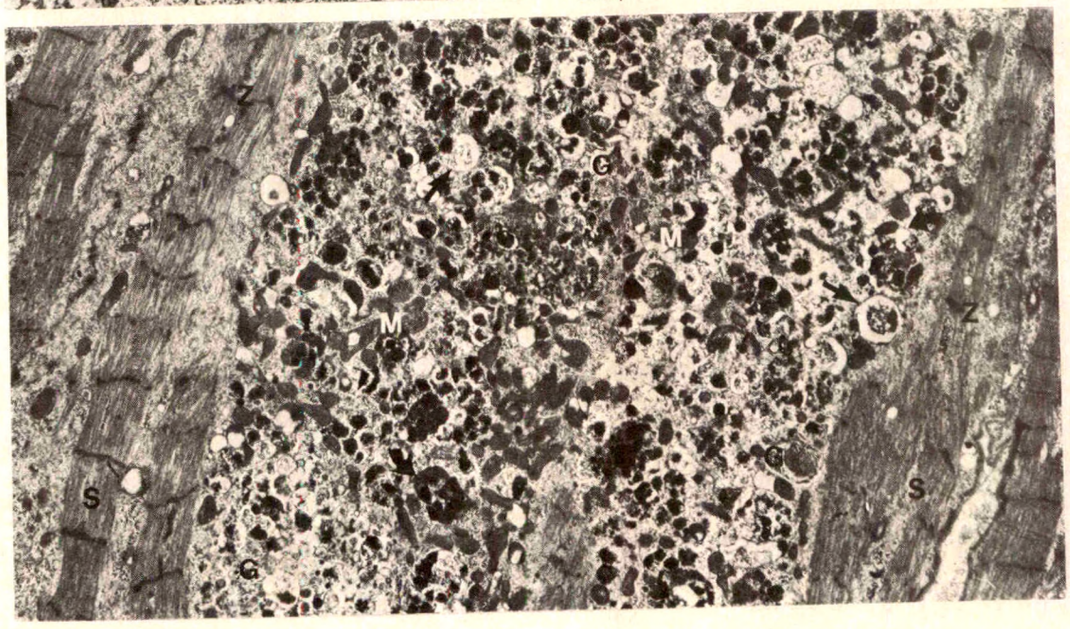


FIGURE 7. Case 14. **Left,** severely degenerating cell isolated by abundant collagen (C) from the surrounding cells. The cytoplasm is devoid of myofilaments and filled with collapsed sarcoplasmic reticulum tubules, glycogen (G) and mitochondria (M). The mitochondria are aggregated at the periphery and elongated. The sarcolemma and basement membrane are normal. Against the sarcolemma are focal accumulations of abnormal Z band material (**arrows**) associated with disordered myofilaments. No well formed sarcomeres are identified. **Below,** a small portion of a cell with "lysosomal degeneration." The central portion of the cell is filled with dense bodies that occasionally appear to be enclosed by membranes (**arrows**). The dense bodies are associated with irregular mitochondria and aggregates of glycogen. The remaining sarcomeres (S) are disarrayed with loss of thick filaments and thickened Z bands (Z). (×8,100, reduced by 8 percent.)

tients 14 and 15 contained large numbers of myelin figures and dense bodies (Fig. 7, bottom). The dense bodies were variably sized masses of electron-dense material without distinct substructure. Clusters of this material were frequently enclosed by membranes. These clusters of presumably lysosomal digested organelles were frequently located in the central area of the cells and were bordered by normal myofibrils. Similar accumulations of myelin figures and dense bodies have been reported in the left atrium of patients with mitral valve disease.[3]

Discussion

Role of increased right atrial flow in presence of normal pressure: This study did not demonstrate any relation between increased right atrial blood flow and the development of structural changes in the right atrium. In the 12 patients with increased right atrial blood flow and normal mean pressure (Group I) there were no significant structural changes in the tissue available for study. Accumulations of abnormal Z band material were present, but in less than 5 percent of the cells examined, in 8 of these 12 patients. Z band changes have been reported in both diseased[3–6] and normal atrial cells.[1,7] Although Z band changes are frequent in hypertrophied atrial cells,[1] they appear to be nonspecific changes and are apparently not indicative of either cell hypertrophy or degeneration. Irregular intercalated discs with increased amounts of associated fibrillar material were also found in 6 of these 12 patients but in less than 1 percent of the cells examined. Although we have previously interpreted this type of change as an indicator of cell hypertrophy,[1] there was no other structural evidence of cell hypertrophy[1,8] and cell size was within normal range in all six patients. These same disc changes were found with increased frequency in the hypertrophied cells of patients in Group II with elevated right atrial pressure (more than 20 percent of the cells examined). Such intercalated disc changes, although not specific for cell hypertrophy, are clearly more prominent in hypertrophied right atrial myocardial cells.

We previously determined that the right atrium of patients with ventricular septal defect is structurally normal.[1] Except for the rare intercalated disc and Z band changes, the right atrium in the 12 patients with normal right atrial mean pressure but increased blood flow was ultrastructurally identical to the atrium in patients with ventricular septal defect and, therefore, presumably normal. These findings are in contrast to the structural changes previously reported in the right atrium of patients with both increased right atrial blood flow and mean pressure, who had changes of both cell hypertrophy and degeneration.[1] Similar structural changes were found in the three patients in Group II with increased right atrial blood flow and mean pressure. The presence of an atrial septal defect, therefore, does not in some way prevent the development of structural changes in the right atrium. Rather, the development of structural changes appears to depend on whether or not right atrial pressure is increased. We were unable to determine if increased right atrial pressure alone is related to the development of structural changes or whether these changes are related to increased right atrial pressure in the presence of increased right atrial blood flow. However, this study has shown that increased right atrial blood flow alone is not related to the development of structural changes in the right atria.

Role of increased right atrial pressure with increased blood flow in hypertrophy and degeneration: Nine patients with increased right atrial mean pressure and blood flow (three patients in Group II of this study plus six patients with endocardial cushion defect[1]) constitute too small a sample to evaluate whether the magnitude of increased pressure in the right atrium is related to the development of structural changes. Although only four of these nine patients had degenerative changes, the marked degenerative changes were found in the patients with the highest right atrial mean pressure (Patients 14 and 15 of this study and the two patients with the most pronounced elevations of pressure in our previous study.[1]) The suggestion is that pressure elevation is directly related to the development of degenerative changes. In contrast, changes of hypertrophy were present in all three patients in Group II of this study, as well as in all six patients with endocardial cushion defect.[1] We have demonstrated that increased blood flow alone is not related to structural changes in the right atrium; therefore, hypertrophy of the right atrium may be secondary to slight increases in right atrial pressure or the result of slightly increased pressure in the presence of increased blood flow.

Role of pulmonary hypertension: Seven of the patients in Group I and the three patients in Group II had a large atrial septal defect, as indicated by a pulmonary to systemic blood flow ratio of greater than 2.0.[9] In spite of the greatly increased atrial blood flow and large size of the atrial defect, the seven atria of the patients in Group I were structurally normal, whereas there were structural changes in the atria of the three patients in Group II. Similarly, the duration of the increased blood flow did not correlate with the development of structural changes. Patient 12 was 47 years old and had a normal right atrium; Patient 13 had structural changes at age 7 years. In both instances the presence of increased right atrial pressure determined whether structural changes were found in the right atrial myocardium. This increase in right atrial pressure was not directly related to either the magnitude of the shunt or the duration of the shunt; rather, increased atrial pressure appeared to be related to increases in pulmonary atrial pressure. The three patients with increased atrial pressure had elevated pulmonary arterial pressures, whereas the pulmonary arterial pressures in the 12 patients in Group I were normal. The development of increased right atrial pressure in patients with an atrial septal defect is probably secondary to changes in the pulmonary circulation. The increased pulmonary pressure causes an increase in right ventricular pressure with a corresponding decrease in right ventricular compliance. The decreased right ventricular compliance leads to elevation of right atrial pressure.

Atrial arrhythmias: The right atrium was moderately to markedly dilated in all 15 patients in this study, yet none of the patients had atrial arrhythmias. Previ-

ous studies[10,11] have suggested that left atrial dilatation is directly related to the occurrence of atrial arrhythmias. Our results suggest that right atrial dilatation even of marked degree need not be associated with atrial arrhythmias.

Implications: These studies indicate that volume overload of the right atrium in the absence of changes in other hemodynamic factors, such as pressure, does not result in cell hypertrophy or degeneration. Further studies are needed to determine whether the structural changes in the right atrium of patients with congenital heart disease are the result of the increased right atrial pressure or of the combination of increased pressure and volume overload.

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Role of the Renin-Angiotensin-Aldosterone System in Hypertensive Children With Coarctation of the Aorta

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To investigate the role of the renin-angiotensin-aldosterone system as a cause of hypertension, 20 hypertensive patients with coarctation of the aorta were studied during normal and low sodium intake and after diuresis with furosemide. Eight patients with essential hypertension and 13 control subjects were similarly studied. Plasma renin activity values in patients with coarctation were similar to those in patients with essential hypertension and in control patients during normal and low sodium diets. However, after the administration of furosemide, plasma renin activity values were significantly higher in the patients with coarctation than in the other two groups ($P < 0.005$ and < 0.01, respectively). The values for urinary aldosterone, plasma volume and extracell fluid volume (bromide space) were increased in patients with coarctation during both normal and low sodium intake. These renin and aldosterone responses and body fluid spaces in patients with coarctation suggest that their hypertension resembles a one-kidney Goldblatt model. The data help to better define the role of the renin-angiotensin-aldosterone system in the hypertension of coarctation and thus may help guide the clinician in therapeutic interventions.

Systemic hypertension is common in coarctation of the aorta. The cause is not known. Previous studies[1–4] attempted to define whether an abnormality of the renin-angiotensin-aldosterone system is the cause of such hypertension. Our hypothesis is that initially the coarctation decreases renal blood flow; this hypoperfusion stimulates the juxtaglomerular apparatus to secrete renin[5] and thereby increases the production of angiotensin and aldosterone, hormones that stimulate renal retention of sodium and water.[6] The resulting expansion of blood volume and extracell fluid volume increases blood pressure, which tends to correct the decreased renal perfusion. Simultaneously, feedback inhibition of the excessive renin secretion occurs.[5] We believe that coarctation is analogous to the one-kidney Goldblatt model of hypertension[7]: once renal perfusion is restored to normal, plasma renin activity returns to normal.[8] In previous studies,[8,9] when patients with coarctation were maintained on a low sodium diet and given diuretic therapy, plasma renin increased.

In an attempt to prove our hypothesis, we studied hypertensive patients, with either coarctation or essential hypertension, and control subjects during normal and reduced sodium intake and after further acute sodium depletion with furosemide.

Methods

Patients: The patients studied were older than 3 years of age and attended the Cardiology or Nephrology Clinic at the Hospital for Sick Children at some time from January 1976 through September 1977 because of coarctation with hypertension or essential hypertension. Informed consent was obtained from all patients or their parents. As in our previous study,[10] hypertension was defined

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as blood pressure greater than two standard deviations above the mean value from the data of Londe[11] or The Society of Actuaries.[12] Essential hypertension was defined as an increase in blood pressure in the same range for which no cause could be found after the patients had had a complete cardiac, renal and endocrine evaluation, including renal arteriography.

Twenty patients with coarctation, 8 patients with essential hypertension and 13 control subjects were studied. The hypertensive patients were classified into four groups according to diagnosis, and the control subjects were classified according to age (Table I). Before the start of the study, a dietitian and a metabolic nurse visited each patient's home to assess whether a low sodium diet would be feasible as an outpatient procedure. Parents and patients were instructed how to keep dietary records and collect 24 hour urine samples.

Study protocol (Table II): Urinary and plasma sodium and potassium levels were determined with standard flame photometry (model 143, Instrumentation Laboratory, Lexington, Massachusetts), and urinary and plasma creatinine levels were determined with an Auto Analyzer (Technicon, New York, New York). Urinary aldosterone was measured with the double isotope dilution derivation technique,[14] and values were plotted in relation to urinary sodium excretion, using the nomogram devised by New et al.[15] Blood was drawn for plasma renin activity with the patient in the sitting position after 3 hours of ambulation. Plasma renin activity[16,17] and plasma aldosterone[18] were measured with the radioimmunoassay technique. Radionuclide plasma volume was determined with ^{131}iodine-labeled serum albumin.[19] Extracell fluid volume was estimated by measuring the plasma bromide in duplicate samples, with neutron-activation analysis on the SLOWPOKE reactor at the University of Toronto; the error in determination is less than 2 percent.[20] Results were normalized by conversion to percent of predicted value from the microdiffusion technique of Cheek.[21,22]

Salt restriction to 10 mEq/day of sodium required major dietary constraints: for example, the diet did not permit milk and required the inclusion of salt-free bread and margarine. Therefore, much of the necessary food was provided by the

TABLE I

Study Groups

Group no.	no. of Cases	Definition	Age (yr)	Sex Ratio (male/female)
I	12	Untreated COA + upper limb hypertension	3.5–20	17/3
II	6	Recoarctation ≥ 1 yr after resection		
III	2	Persistently elevated BP; no recoarctation ≥ 1 yr after resection		
IV	8	Essential hypertension*	7–19	...
Va	6	Control subjects (children)*	5–15	1/5
Vb	7	Control subjects (adults)*	22–40	3/4

* Underwent limited protocol: see Table II.
BP = blood pressure; COA = coarctation of the aorta.

TABLE II

Study Protocol

Time	Patient Groups	Investigations	Indexes
Days 0–3	All	Three 24 hr urine collections, starting at noon	Na, K, Cl, creatinine, aldosterone
	I–IV	Record diet	Na intake
Day 3	All	9 A.M.: CIU	Physical examination, including height and weight (for surface area calculation)
	I–III	10 A.M.: radionuclide study	Plasma volume
	All	Noon (end of urine collection):	
	All	a. Blood drawn	Serum Na, Cl, creatinine: PRA
	I–III, V		Plasma aldosterone
	I–III		Plasma bromide (blank)
	I–III	b. BP recorded with Doppler flowmeter	BP in arm and leg, standing and supine
	I–III	c. Infusion of NaBr, iv, for 3 min (NaBr 3%, 1 ml/kg; maximum, 40 ml)	
	I–III	3 P.M.: blood drawn	Plasma bromide
Days 4–13	All	Days 4–10, at home; day 10 to end of protocol, in CIU	Low Na diet (0.3 mEq/kg; maximum, 10 mEq)
Days 8–10*	All	Protocol as for days 1–3	
Day 11	I, II	Cardiac catheterization; premedication with meperidine, chloropromazine and promethazine[13]	a. Routine hemodynamic indexes b. Fick and dye determinations of CI with O_2 consumption c. Angiographic determination of ejection fraction
Day 12†	All	6 P.M., midnight‡ furosemide po,	
Day 13†	All	6 A.M.‡ 1 ml/kg (maximum 40 mg/dose) 9 a.m.: weight and BP (supine) recorded. Then blood drawn. Patient returned home	PRA and plasma aldosterone

* Groups III, IV and V then proceeded to the day 12 protocol.
† Days 10 and 11 for groups IV and V.
‡ Group V (control patients) took these doses at home; they remained ambulant after the 6 A.M. dose and returned to the clinical investigation unit by 8:30 A.M.
BP = blood pressure; CI = cardiac index; CIU = clinical investigation unit; Cl = chloride; iv = intravenously; K = potassium; Na = sodium; NaBr = sodium bromide; po = orally; PRA = plasma renin activity.

TABLE III

Plasma Renin Activity (ng angiotensin I/ml per hour)*

Group no.	Normal Diet		Low Sodium Diet		After Furosemide	
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
I	2.61 ± 2.84	0.80 – 11.19	2.68 ± 1.47	0.91 – 5.24	26.24 ± 18.83	6.44 – 54.48
II	2.00 ± 0.95	0.86 – 3.22	6.07 ± 2.99	1.36 – 8.85	21.51 ± 10.25	5.19 – 31.30
I & II	...	...	...	...	24.60 ± 16.22	...
III	2.49 ± 0.55	2.10 – 2.88	5.34 ± 1.14	4.53 – 6.14	9.40 ± 1.84	8.10 – 10.70
IV	2.02 ± 2.45	0.63 – 7.77	3.54 ± 3.44	0.55 – 11.46	8.71 ± 5.12	5.67 – 20.64
V†	1.30 ± 0.78	0.37 – 2.96	4.83 ± 2.73	0.80 – 10.88	10.61 ± 5.11	3.06 – 19.74

* Data on the individual patients are available from the authors on request.
† Mean values, standard deviations and ranges did not differ significantly in subgroups Va and Vb.
SD = standard deviation.

dietitian on day 3. Compliance with the diet and the adequacy and accuracy of urine collections at home were assessed by reviewing the dietary records, the urinary sodium excretion values and the urinary creatinine values (the average for the three collections was compared with the predicted value for body weight; the minimal normal value was 15 mg/kg per day[23]). The glomerular filtration rate was estimated from the clearance of endogenous creatinine.

At cardiac catheterization, dye-dilution curves were determined after the injection of indocyanine green into the main pulmonary artery; blood was withdrawn from the left ventricle and passed through a Waters cuvette (model DCU 303, Waters Instruments, Rochester, Minnesota), and the area under the disappearance curve was calculated.[24]

We analyzed the results by calculating the mean and one standard deviation. The P values were calculated according to Cochran's modification of the t test if variances were unequal.[25] A P value greater than 0.05 was not significant.

Results

Compliance with low sodium diet: Twelve of the 18 patients in groups I and II and all 10 patients in groups III and V complied with sodium restriction, as reflected by the urinary sodium values. In the other six patients urinary sodium decreased greatly, and the body fluid spaces of these patients (see below) did not differ from those of the other patients in their groups; therefore all data were analyzed together. The inspection of urinary creatinine values to determine completeness of urine collections revealed only one instance of an unexpectedly low value (Patient 3, 94 percent of the predicted value). Because this patient's urinary sodium was quite low, we believed that his compliance with the diet was good and included his data in the analysis.

TABLE IV

Matrix of Intergroup Differences (P Value by t Test)* in Plasma Renin Activity After Administration of Furosemide

Group no.	II	III	IV	V
I	NS	0.025	0.05	0.025
II	...	NS	0.13	0.05
I & II	...	NS	0.005	0.01
III	...	...	NS	NS
IV	..	...	...	NS

* Adjusted by Cochran's test[25] because of unequal population variances.
NS = not significant.

Renin values (Table III): On normal and sodium restricted diets and after the administration of furosemide, the mean renin values for normal pediatric subjects did not differ significantly from those for normal adult subjects. These values were therefore combined for further analyses.

There was no statistically significant intergroup difference in renin values during normal diet; however, during sodium restriction the mean renin value for group I patients differed significantly ($P < 0.05$) from the mean values for groups II and V. After the administration of furosemide, the renin values in patients with coarctation differed significantly from the values in patients with essential hypertension ($P < 0.005$) and in control subjects ($P < 0.01$) (Table IV).

Creatinine values: The creatinine clearance values for patients in groups I, II and III were 94 ± 32, 106 ± 38, and 110 ± 40 ml/min per 1.73 m^2, respectively. In four patients, three in group I and one in group II, the value for creatinine clearance was two standard deviations below the mean value for normal children[26]; their plasma creatinine values were 0.8, 0.8, 0.6 and 0.6 mg/dl, respectively. No patient had a plasma creatinine value greater than the normal value.

Aldosterone values: The values for groups I, II, III and V were similar during the ingestion of normal and low sodium diets and after the administration of furosemide (Table V), but within each group the values increased with increasing sodium depletion. However, during a normal diet in all but one patient with coarctation, the urinary aldosterone values (Table VI) were higher than would be predicted from urinary sodium excretion[15] (Fig. 1).

Body fluid spaces: Radionuclide plasma volume (normal 43 ± 5 ml/kg) was increased in 9 of 11 patients in group I, in 2 of 6 patients in group II and in 1 patient in group III during a normal sodium diet (Table VII). After dietary sodium restriction plasma volume was still increased in all 11 patients in group I and in the same patients in groups II and III. There was no significant intragroup change in plasma volume with a low sodium diet. Groups I and II differed significantly ($P < 0.02$) on day 10.

The extracell fluid volume (bromide space) was greater than that predicted from the data of Cheek[22] in 11 of 12 patients in group I, in 3 of 6 patients in group II and in 1 patient in group III during a normal sodium

diet. After dietary sodium restriction, bromide space remained increased in 8 of 11 patients in group I, in 3 of 6 patients in group II and in the same patient in group III.

Five patients (Cases 6 to 9 and 16) had high values (greater than 21 mEq/day of sodium) for urinary sodium excretion during the sodium-restricted diet; the values for bromide space and plasma volume in these patients did not differ significantly from values in the other patients within their respective groups. The values for these patients were included in all calculations.

Resting and catheterization hemodynamics: The mean systolic leg blood pressure in the supine position for group I (unoperated coarctation) patients was 92 ± 16 mm Hg. This value did not differ significantly from that in group II (recoarctation) patients (112 ± 28 mm Hg). There was no correlation between the resting upper limb systolic pressure and either cardiac index at catheterization or plasma renin activity after the administration of furosemide.

At cardiac catheterization, no patient had left heart failure. The indocyanine green dye-derived cardiac index (normal, 2.8 to 3.6) was 4.7 ± 1.0 liters/min per m^2 in group I and 3.6 ± 0.6 in group II. The mean gradient across the coarctation in group I (42 ± 12 mm Hg) did not differ significantly from that in group II (31 ± 19 mm Hg). In addition, the left ventricular ejection fraction did not differ significantly between groups I and II (0.74 ± 0.09 versus 0.81 ± 0.06, respectively).

Discussion

Renin Values

Several investigators have reported plasma renin values for healthy children on unrestricted diets: for example, 2.37 ± 0.57 ng/ml per hour (mean ± standard deviation) in children aged 2 to 4 years, and 1.48 ± 0.17 in those aged 5 to 6 years,[27] and 2.5 ± 0.5 for 3 to 6 year olds.[28] In one of the few published studies of renin levels in healthy children on low sodium diets, Potter et al.[29] found levels of 4.3 to 15.7 ng/ml per hour during ingestion of a diet containing 20 mEq/day of sodium. Because renin values in adults are similar to those in children over age 6 years[30] we were able to include adults in our control group. In our study, 35 of the 41 subjects were older than age 6 years. With the assay method we used, renin values for healthy adults on normal and low sodium diets are 2.75 ± 2.07 and 6.03 ± 2.07 ng/ml per hour, respectively.

TABLE V

Plasma Aldosterone Values

Group	Case no.	Plasma Aldosterone (ng/dl) Normal Diet	Sodium Restriction	After Furosemide
I	1	47.4	83.4	97.2
	2	15.6	16.8	29.4
	3	19.0	18.3	42.9
	4	12.6	...	...
	5	19.1	20.8	33.7
	6	15.3	90.6	127.8
	7	15.0	13.8	28.2
	8	16.2	25.6	59.7
	9	15.0	18.9	43.7
	10	19.8	31.8	34.3
	11	28.8	48.6	...
	12	55.5	32.0	134.4
Mean ± SD		23.3 ± 13.9	36.4 ± 26.9	63.1 ± 41.2
II	13	17.6	61.8	81.0
	14	22.8	33.0	63.6
	15	19.6	48.4	61.6
	16	21.6	19.8	...
	17	25.5	52.8	40.8
	18	16.8	34.2	137.4
Mean ± SD		20.7 ± 3.3	41.7 ± 15.4	76.9 ± 36.7
III	19	15.6	39.6	50.5
	20	11.8	49.3	66.6
Mean ± SD		20.7 ± 3.3	41.7 ± 15.4	76.9 ± 36.7
Mean ± SD		13.7 ± 2.7	44.5 ± 6.7	58.6 ± 11.4
IV	21–28	...	...	...
Va	29	12.0	52.2	67.2
	30	13.2	93.0	158.4
	31	15.6	...	...
	32	14.4	49.8	94.2
	33	16.6	58.2	60.2
	34	9.6	27.0	57.0
Vb	35	31.2	77.4	40.8
	36	15.6	109.2	108.0
	37	18.3	71.5	78.3
	38	15.6	30.0	45.0
	39	9.9	77.1	...
	40	15.6	38.7	51.6
	41	16.2	33.3	51.3
Mean ± SD		15.7 ± 5.3	57.5 ± 29.9	73.8 ± 34.9

SD = standard deviation.

Markiewicz et al.[31] recorded renin values in 10 healthy children after 1 day of sodium restriction followed by the administration of furosemide (40 to 80 mg orally, in two divided doses). However, their use of a 3 hour incubation period in the angiotensin I assay precluded comparison with our study. A comparison of

TABLE VI

Urinary Aldosterone and Radionuclide Plasma Volume Values*

Group no.†	Urinary Aldosterone (μg/m^2 per day) Normal Diet	Sodium Restriction	Radionuclide Plasma Volume (ml/kg) Normal Diet	Sodium Restriction
I	27.8 ± 15.7	96.2 ± 77.5	52.3 ± 3.4	53.0 ± 4.8
II	20.2 ± 17.2	107.2 ± 3.84	47.9 ± 8.0	46.0 ± 6.0
III	56.1 ± 9.1	121.8 ± 100.8	45.7 ± 16.6	48.2 ± 17.7

* Data on the individual patients are available from the authors on request.
† Measurements were not performed in patients in groups IV and V.
Data are expressed as mean values ± standard deviations.

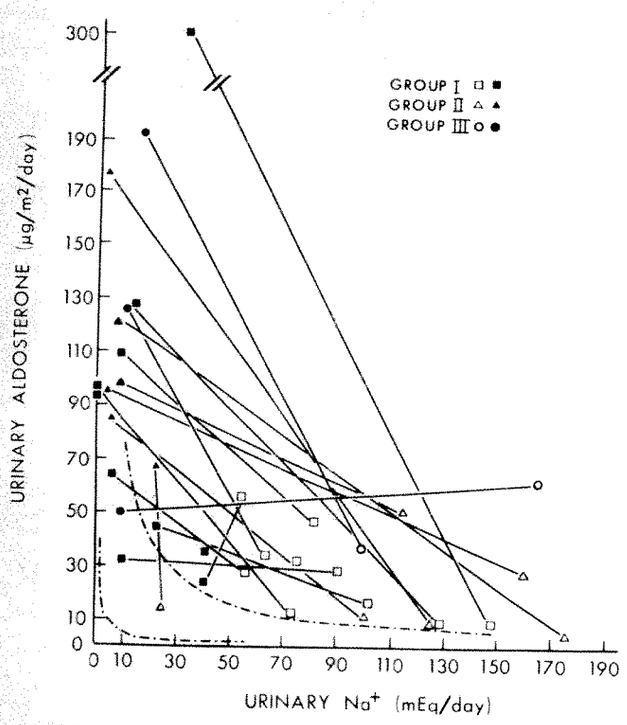


FIGURE 1. Urinary aldosterone in relation to urinary sodium in patients with coarctation, plotted according to the nomogram devised by New et al.[15] The **broken lines** represent the 5th and 95th percentiles. The **open symbols** represent a normal diet and the **closed symbols** a low sodium diet. See Table I for an explanation of groups I, II and III.

renin values after the administration of furosemide in hypertensive children with coarctation with the values in our control subjects dislosed that abnormal hypersecretion of renin occurred in the hypertensive children in response to furosemide administered after a period of sodium restriction. Furthermore, the renin response in the hypertensive children with coarctation differed from that in our age-matched group of patients with essential hypertension. The increase in plasma renin produced by sodium restriction was not as marked as the increase produced by diuresis with furosemide. Previous work[32] described a nonsodium-related mechanism of renin release after the administration of furosemide.

Aldosterone Values

The plasma aldosterone values are difficult to interpret. There is one report[33] on plasma aldosterone in children during an unrestricted diet, but there are no data on children during a low sodium diet.[34] Mean plasma aldosterone concentration (24.9 ng/dl) does not change appreciably between ages 1 and 15 years. No standard deviations were provided by Kowarski et al.[33] for this wide age range, but inspection of their data reveals that a level greater than 60 ng/dl was unusual. In 17 of the 28 subjects (61 percent) in our series in whom plasma aldosterone was measured after the administration of furosemide, plasma aldosterone values were greater than 60 ng/dl.

The data in our groups I, II, III (coarctation) and V (controls) suggest that the low sodium diet and furosemide were both potent stimuli for aldosterone secretion. Within each group the plasma concentration increased with each degree of sodium depletion. However, there was wide scatter within each group and even in the same patient, a phenomenon observed by Kowarski et al.[33]

The values for urinary aldosterone excretion plotted against the values for urinary sodium excretion (Fig. 1) shows several interesting features. On a normal sodium diet the values for urinary aldosterone in groups I, II and III are greater than the values reported in normal children.[15] However with sodium restriction urinary aldosterone secretion increased further in all patients except one. This increase in aldosterone secretion occurred consistently and may be important in the pathophysiology of hypertension in these patients. The increased aldosterone secretion occurred when the plasma renin level was normal and thus was apparently caused by a stimulus other than renin secretion.

Other known causes for hyperaldosteronism include hyperkalemia, hyponatremia and increased secretion of adrenocorticotropin (ACTH) or angiotensin.[35] None of our patients had an abnormal value for plasma sodium or potassium or metabolic alkalosis. We did not measure ACTH, but we had no reason to expect it to be increased.

Body Fluid Spaces

Our finding of expanded extracell fluid volume with normal sodium intake in patients with coarctation supports our hypothesis that coarctation may resemble the one-kidney Goldblatt model for hypertension. Mean extracell fluid volume was 120 percent of the value predicted by Cheek's nomogram[12] in group I (unoperated), 111 percent in group II (recoarctation) and 109 percent in group III (persistent hypertension without recoarctation).

The bromide assay developed recently at this center has excellent validity compared with standard assays.[21,22] The value for the bromide space on day 10 did not always decrease from the day 3 value. The retention of bromide, causing high "blank" values in the second week's determination, may have impaired the accuracy of the second measurement.

Plasma volumes measured with the radionuclide technique were increased significantly during a normal diet in group I patients, increased mildly in group II patients and were normal in group III patients. The plasma volume did not change significantly from the first to second determinations, possibly suggesting again that 1 week of dietary sodium restriction caused insufficient sodium depletion to produce plasma volume contraction. We did not repeat the determinations of extracell fluid and plasma volumes after the administration of furosemide, but we observed a mean weight reduction of 1.07 kg in the patients in groups I to III, reflecting volume contraction.

For many reasons the accurate measurement of body fluid compartments is difficult. However, in our un-

treated patients with coarctation (group I), extracell fluid volume, plasma volume and post-furosemide plasma renin activity consistently were increased. These measurements were less consistent in group II patients (recoarctation). The reason for this difference in the two groups of patients is not known but might be related to age, to the duration and severity of renal hypoperfusion or to a renal insult at the time of cardiac surgery in the group II patients.

Clinical Implications

Similarity to one-kidney Goldblatt model of hypertension: We demonstrated that in patients with coarctation and hypertension the cardiac index was increased and the renin response to severe sodium depletion differed from that in control subjects or patients with essential hypertension. Also in our patients with coarctation, urinary aldosterone excretion was inappropriately high for sodium intake, and plasma aldosterone increased above normal with sodium restriction. These observations support our view that coarctation resembles the early phase of a one-kidney Goldblatt model of hypertension, in which reduced renal perfusion causes an initial increase in plasma renin. The ensuing fluid-volume expansion and increased cardiac index replace increased renin secretion as the cause of the increased arterial pressure. However, in Goldblatt's chronic one-kidney model, cardiac index and body fluid space measurements decrease toward normal values and increased systemic vascular resistance becomes the major cause of hypertension.[7]

However, all of these features were not present in our hypertensive patients with coarctation. Although the arterial pressure distal to the coarctation returned to normal, our patients did not achieve the chronic steady state of normal plasma renin secretion, normal cardiac index, normal body fluid spaces and increased systemic vascular resistance. This may be related to the differences in the development of systemic collateral circulation in patients with coarctation and those with renal arterial stenosis.

Therapeutic implications: An angiotensin II blocking agent[36] was demonstrated to decrease blood pressure in patients with coarctation. We predict that an angiotensin converting enzyme inhibitor[37] would do the same. This decrease in systemic blood pressure would be useful for diagnosis but would probably not be useful for the long-term management of these patients.

TABLE VII

Percent of Predicted Extracell Fluid Volume (Bromide Space)*

Group†	Normal Diet: Percent of Predicted Bromide Space	Sodium Restriction: Percent of Predicted Bromide Space
I	120 ± 17	117 ± 24
II	111 ± 30	96 ± 21
III	109 ± 13	118 ± 35

* Data on the individual patients are available from the authors on request.

† Measurements were not performed in patients in groups IV and V.

Values are expressed as mean values ± standard deviations.

Although corrective surgery remains the therapy of choice, the high recurrence rate of coarctation after surgery in infancy and early childhood[10,38–41] make medical management desirable until the patient is old enough for operative repair. Hypertension above the coarctation maintains adequate renal perfusion, and the correction of this hypertension may not be clinically desirable. If therapy of the hypertension is necessary, a beta adrenergic blocking drug with or without a diuretic agent may be useful for decreasing the cardiac index, blocking renin secretion and decreasing extracell fluid and plasma volumes.

Mechanism of persistent hypertension without recoarctation: The patients in group III are important in the study of hypertension in children with coarctation because they represent patients with corrected coarctation and persistent hypertension. We were able to study only two patients in this group. We do not know whether hypertension in such patients is related to an altered renin-angiotensin-aldosterone system, increased sympathetic activity,[42–44] intrarenal or systemic vascular changes,[45] disturbance in "total body autoregulation" of blood flow[46] or an unknown mechanism.

Acknowledgments

We express our gratitude to Eleanor Pask, MScN, for help in patient education and care; Louise Bell, MSc, RPDt, for organization and implementation of the diets; Dr. Paul Keane, McMaster University, Hamilton, Ontario, for the plasma aldosterone assay results; Ursala Matthews for editorial assistance; Lydia Luna, BSc, for the renin measurements; and Diane Misiorowski for secretarial assistance in the preparation of the manuscript.

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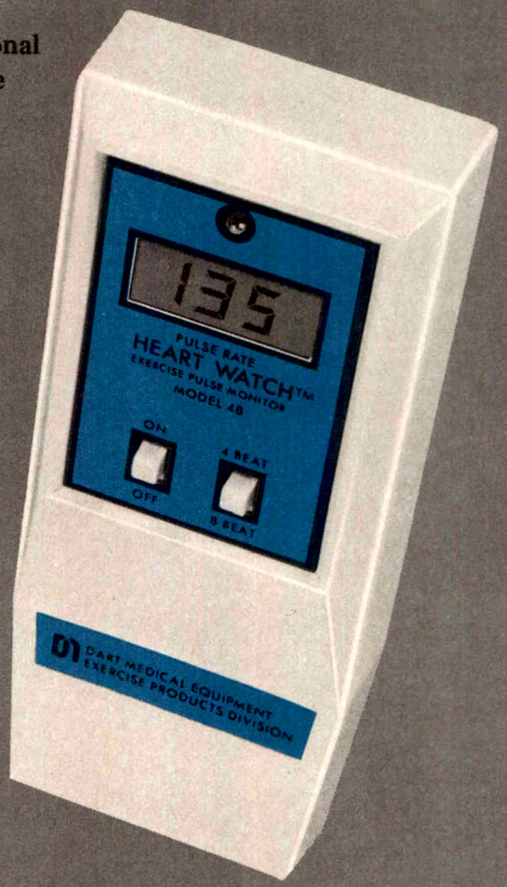
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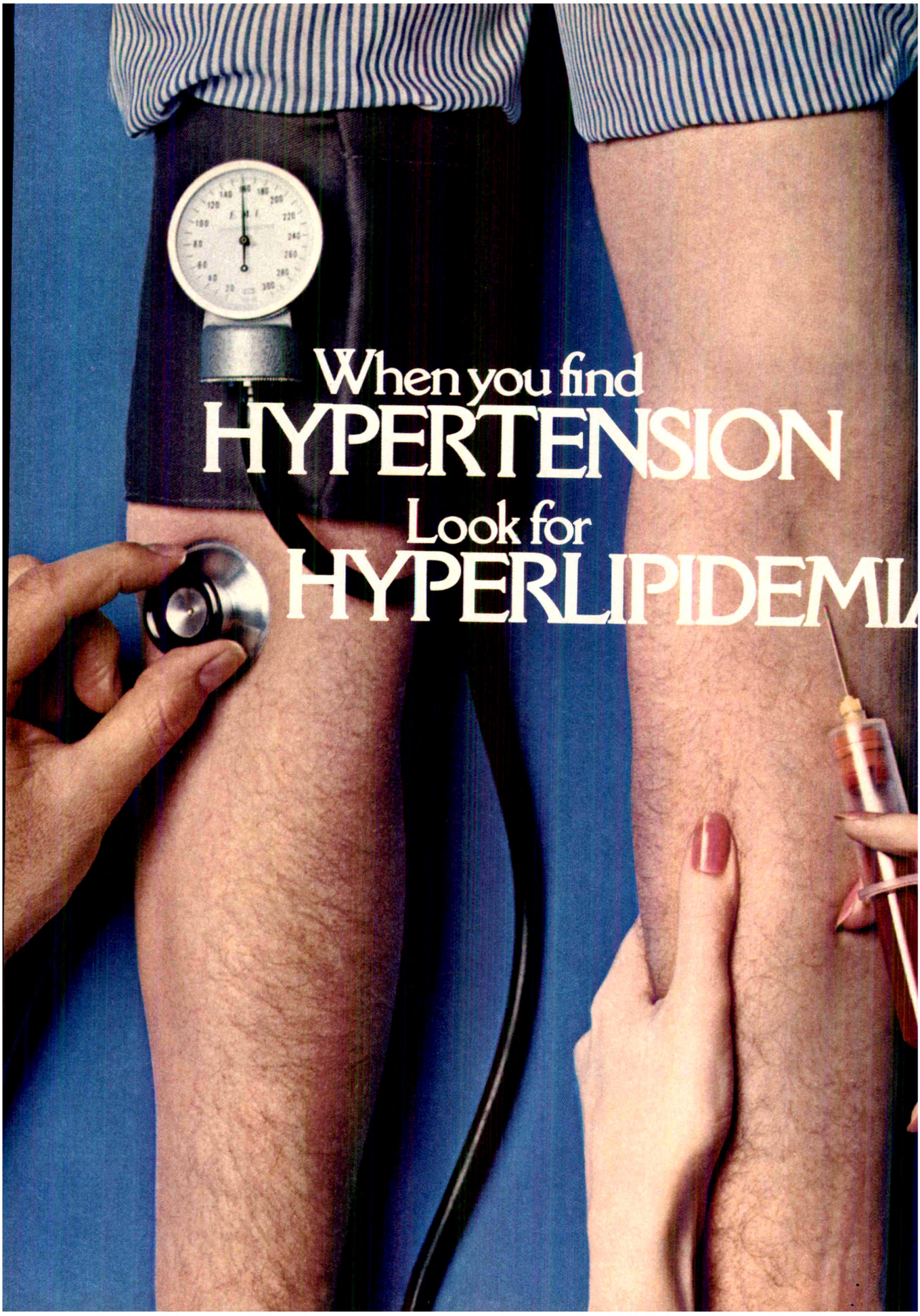
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	Incidence of Hyperlipidemia	
Type of Hyperlipidemia*	Hypertensives (89 subjects)	Normotensives (89 subjects)
Type IIA	9% (8)	7% (6)
Type IIB	6% (5)	3% (3)
Type IV	26% (23)	11% (10)
Total	**41% (36)**	**21% (19)**

*Hyperlipidemia was diagnosed when cholesterol levels exceeded 282 mg% and/or triglycerides were over 177 mg%—cutoff points higher than the usual upper limits of normal.
Adapted from Thomas, G. W., *et al.*[1]

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Today, lipid determinations are recommended as part of every general medical examination.

Because elevated lipids may coexist with high blood pressure, it is especially important to screen hypertensive patients for hyperlipidemia. Testing for both cholesterol *and* triglycerides is considered essential,[2-5] since it increases the chances of detection from 6 out of 10 to 9.5 out of 10.[6]

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

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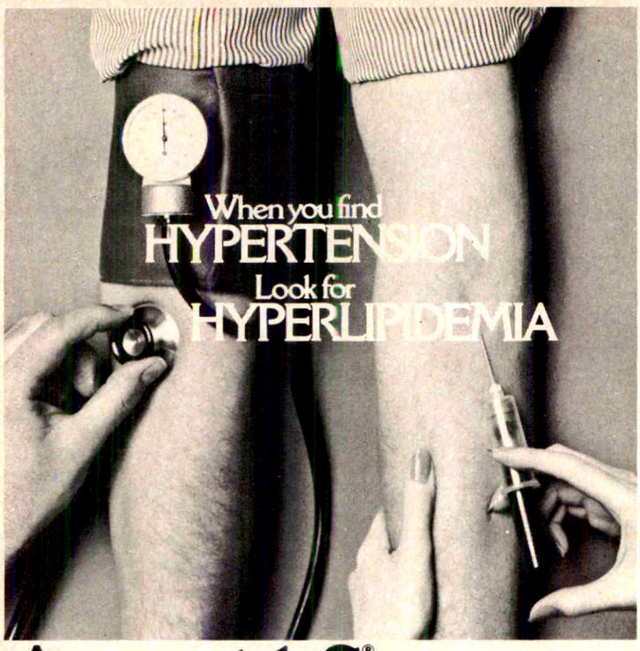
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BRIEF SUMMARY

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INDICATIONS: ATROMID-S is indicated as adjunctive therapy in patients who do not respond adequately to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

Administration of clofibrate to mice and rats in long-term studies at eight times the human dose resulted in a higher incidence of liver tumors than in controls. Lower doses were not studied. Although the relevance of this finding to humans is not known at this time, it cannot be dismissed especially since this drug is intended for long-term administration. ATROMID-S should be used only in patients with hyperlipidemia who do not respond adequately to dietary intervention.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long-term administration of a drug of this nature, adequate baseline studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original baseline may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate, in bottles of 100.

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Conduct
with Pronestyl®
Procainamide Hydrochloride
• documented effectiveness in ventricular arrhythmias; indicated for certain atrial arrhythmias as well
• an effective alternative to lidocaine for intravenous administration
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• unsurpassed versatility—injectable and oral are the same chemical entity, possess the same pharmacodynamics
• produced under exacting quality control standards by Squibb—numerous specific quality control tests from starting material to finished product
See next page for brief summary

PRONESTYL® INJECTION

Procainamide Hydrochloride Injection USP

DESCRIPTION: Pronestyl Injection (Procainamide Hydrochloride Injection USP) is a sterile, aqueous solution providing 100 mg or 500 mg procainamide hydrochloride per ml. The 100 mg/ml potency contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives. The 500 mg/ml potency contains 0.1% methylparaben and not more than 0.2% sodium bisulfite as preservatives.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with oral maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure antinuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported in patients on oral maintenance therapy. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

For full prescribing information, consult package insert.

HOW SUPPLIED: Pronestyl Injection (Procainamide Hydrochloride Injection USP) is available in 10 ml vials providing 100 mg procainamide hydrochloride per ml and in 2 ml vials providing 500 mg procainamide hydrochloride per ml.

PRONESTYL® TABLETS

Procainamide Hydrochloride Tablets

PRONESTYL® CAPSULES

Procainamide Hydrochloride Capsules USP

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative antiarrhythmic therapy.

DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide analogue of procaine hydrochloride and is available for oral administration as veneer-coated tablets and capsules providing 250 mg, 375 mg, and 500 mg procainamide hydrochloride.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamic should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damag normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus h been reported with oral maintenance procainami therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may als occur. Rare cases of thrombocytopenia or Coomb positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure an nuclear antibody titers at regular intervals in patients on procainamide for extended periods c time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (antinuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Ster therapy may be effective if discontinuation of pr cainamide does not cause remission of symptom If the syndrome develops in a patient with recurre life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be us concomitantly with procainamide.

ADVERSE REACTIONS: Hypotension is rare wi oral administration. Serious disturbances of card rhythm such as ventricular asystole or fibrillatior are more common with I.V. administration.

Large oral doses may sometimes produce ano rexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus h been reported in patients on oral maintenance therapy (see Precautions). Reactions consisting fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acu hepatomegaly, and a rise in serum glutamic oxal acetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procai amide therapy; and the patient should be instruct to report any soreness of the mouth, throat or gun unexplained fever or any symptoms of upper res ratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellu depression, procainamide therapy should be dis continued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, wea ness, mental depression, giddiness, psychosis w hallucinations, and hypersensitivity reactions su as angioneurotic edema and maculopapular rash have been reported.

For full prescribing information, consult packa insert.

HOW SUPPLIED: Pronestyl Tablets (Procainami Hydrochloride Tablets) and Pronestyl Capsules (Procainamide Hydrochloride Capsules USP) pr viding 250 mg, 375 mg, and 500 mg procainamid hydrochloride are available in bottles of 100 and Unimatic® single-dose packaging in cartons of 1C The 250 mg and 500 mg tablets and capsules are also available in bottles of 1000.

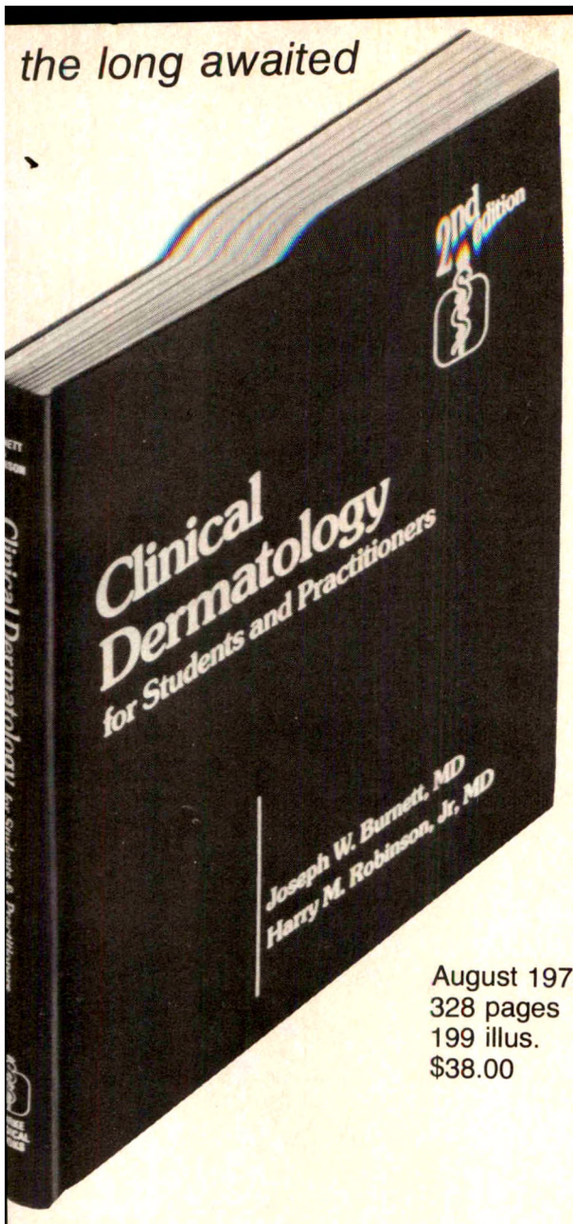
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See third page for brief summary of prescribing information.

Distinguishing Qualities of Dobutrex

Strong Inotropic Activity through Selective Stimulation

Dobutrex is a potent, positive inotropic agent whose primary activity results from stimulation of the β receptors of the myocardial muscle cells.[1]

Hemodynamic Improvements

Dobutrex has minimum effect on the adrenergic receptors in the vasculature.[1] In most patients, blood pressure changes are small, and decreases in afterload and preload have been reported in clinical investigations (see warnings).[2]

Small Effect on Heart Rate and Automaticity

Dobutrex has minimum effect on ventricular automaticity[3] and does not reduce blood pressure.[4] This, together with its low chronotropic potential, reduces the risk of arrhythmia (see warnings).

Renal Output and Urine Flow

Dobutrex does not have the direct renal vasodilative effect of low-dose dopamine; however, in patients with heart failure, Dobutrex generally promotes a diuresis as renal perfusion rises with the increased cardiac output.[5]

Direct-Acting

Unlike dopamine, Dobutrex acts directly on the myocardium and does not depend on the release of endogenous norepinephrine for its inotropic activity.

Myocardial Oxygen Balance

Increases in coronary heart perfusion due to increased cardiac output, together with a favorable influence on some of the major determinants of oxygen consumption (for example, decreases in left-ventricular filling pressure, decreases in systemic vascular resistance, and a mild chronotropic effect [2,6]), suggest that Dobutrex improves or maintains myocardial oxygen balance.

Infrequent Side Effects

Increases in heart rate, blood pressure, and ventricular ectopic activity have occurred. The drug is contraindicated in patients with idiopathic hypertrophic subaortic stenosis. In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used before therapy with Dobutrex is instituted. For warnings, precautions, and adverse reactions, see the brief summary of prescribing information.

Because of the rapid onset and brief duration of action of Dobutrex, precise adjustment of cardiac stimulation is possible by regulation of the rate of administration. As a result, when undesirable effects arise, temporary discontinuation of the infusion or reduction in dosage will generally reverse the adverse conditions. No additional remedial measures are usually necessary.

References:
1. Circ. Res., 36:195, 1975.
2. Circulation, 55:375, 1977.
3. Anesthesiology, 44:281, 1976.
4. Intensive Care Med., 3:57, 1977.
5. Circulation, 56:468, 1977.
6. Br. Heart J., 37:629, 1975.

Dobutrex®

Lilly

Dobutamine HCl



For I.V. Injection
250 mg* in 20-ml vials
*Equivalent to dobutamine

Please see following page for brief summary of prescribing information.

Eli Lilly and Company
MC-897
P.O. Box 618
Indianapolis, Indiana 46206

Please send me additional information regarding Dobutrex® (dobutamine hydrochloride, Lilly).

Name

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900288

Dobutrex®
Dobutamine HCl



Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051 Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient. [081678]

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Additional information available to the profession on request.

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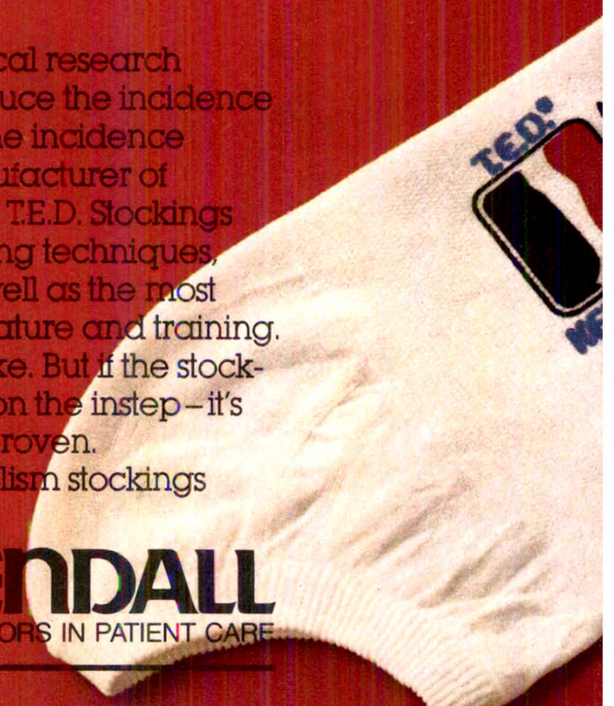
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   c. gangrene,
   d. recent skin graft.
2. Severe arteriosclerosis or other ischemic vascular disease.
3. Massive edema of legs or pulmonary edema from congestive heart failure.
4. Extreme deformity of leg.
5. For thigh length, patients with a circumference greater than 25 inches (63.5cm) at the gluteal furrow. For full leg (X-S, S, M, L), patients with a circumference of 25 inches (63.5cm) or greater at the gluteal furrow. For full leg (X-L), patients with a circumference of greater than 32 inches (81.3cm) at the gluteal furrow.

Precautions:

1. Proper sizing and application must be assured.
2. For full leg style T.E.D.® Stockings, avoid interference of side panels or waistband with incisions, drainage tubes, catheters or other exterior devices.

Warnings:

Caution: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.

Footnotes:

1. Holford, C.P., "Graded Compression for Preventing Deep Venous Thrombosis." **British Medical Journal, 2**: 969-970, 1976.
2. Scurr, J.H. et al., "The Efficacy of Graduated Compression Stockings in the Prevention of Deep Vein Thrombosis." **British Journal of Surgery, 64**: 371-373, 1977.
3. Barnes, Robert W. et al., "Efficacy of Graded-Compression Antiembolism Stockings in Patients Undergoing Total Hip Arthroplasty." **Clinical Orthopaedics, 132**: 61-67, 1978.
4. Wilkins, Robert W. et al., "Elastic Stockings in the Prevention of Pulmonary Embolism: A Preliminary Report." **New England Journal of Medicine, 246**: 360-364, 1952.
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Meyerowitz, B.R., & Nelson, R., "Measurement of Velocity of Blood in the Lower Limbs with and without Compression." **Surgery, 56**: 481-486, 1964.

Sigel, Bernard, et al., "Compression of the Deep Venous System of the Lower Leg During Mactine Recumbering." **Archives of Surgery, 106**: 38-43, 1973.

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Coarctation of the Aorta: Review of 234 Patients and Clarification of Management Problems

RICHARD R. LIBERTHSON, MD
D. GLENN PENNINGTON, MD
MARSHALL L. JACOBS, MD
WILLARD M. DAGGETT, MD, FACC

Boston, Massachusetts

Two hundred thirty-four patients with coarctation of the aorta who were managed between 1948 and 1978 were reviewed. Their ages ranged from 1 day to 72 years. Only 6 percent of the patients who had surgical correction between ages 1 and 5 years had residual hypertension. In contrast, 21 percent of those operated on before age 1 year (all with residual or recurrent coarctation), 30 percent of those operated on between ages 6 and 18 years, 47 percent of those operated on between ages 19 and 40 years and 50 percent of patients over 40 age years at the time of operation had residual postoperative hypertension. These data suggest that the optimal time for elective surgical correction of coarctation is between the ages of 1 and 5 years.

Preoperative congestive heart failure was present in 67 percent of patients under age 1 year, in 67 percent of those over age 40 years and in only 4 percent of those aged 1 to 40 years. Eight of the 29 infants with preoperative heart failure had residual postoperative failure related in most to associated congenital cardiac anomalies. Six of the 16 patients with preoperative heart failure who were over age 40 years at correction had residual failure, although even in these patients heart failure was improved. Bacterial endocarditis, cerebral vascular accident, myocardial infarction and aortic dissection were present in 2, 6, 3 and 2 percent of patients, respectively; these complications occurred more frequently with advancing age and occurred in 13 patients who had had prior coarctation repair.

Additional congenital heart lesions were present in 34 percent of the patients. Of those under age 1 year, 67 percent had a clinically significant patent ductus arteriosus with or without ventricular septal defect or aortic stenosis. After age 1 year, 27 percent of the patients had associated cardiac lesions, and no patient had a clinically significant patent ductus or ventricular septal defect. Aortic stenosis or insufficiency was present in 33 patients. When identified during infancy, aortic stenosis was often clinically significant. Thereafter, only eight patients had clinically significant aortic valve disease at the time of this review, and only two of these patients were younger than age 40 years.

In spite of the extensive medical and surgical experience with coarctation of the aorta,[1-50] there are still unanswered questions pertaining to the management of patients with this condition. The most important question concerns the optimal timing of elective coarctation repair, with reference to the increased incidence of residual coarctation when surgery is performed in infancy versus increasingly frequent residual hypertension when surgery is performed later in life.[16] Although many authors favor elective repair early in childhood,[2-11] few data are available on the actual incidence of postoperative hypertension when correction is performed at different ages. Furthermore, although attention was directed by the National Task Force on Blood Pressure Control in Children to

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the fact that hypertensive blood pressure may be considerably lower in children than in adults, blood pressure in children with postoperative coarctation was not previously assessed with these criteria.[51]

The efficacy of surgery in the older patient with coarctation who already has established hypertension and may have acquired complications, including congestive heart failure, is still controversial,[5,7,9,12-16] and little data are available on the incidence of residual hypertension or failure in these older patients. Finally, although associated congenital heart lesions have been well described,[3,4,8,9,17-26] including the frequent occurrence of bicuspid aortic valve, the clinical significance of these associated lesions still warrants discussion.

Methods

In this study we reviewed the records and follow-up course of 234 patients treated at the Massachusetts General Hospital from 1948 to 1978 who had coarctation of the aorta diagnosed at cardiac catheterization, surgery or postmortem examination. The history, physical examination, electrocardiograms, chest roentgenograms, cardiac catheterization and angiographic data, surgical and autopsy findings when available, and follow-up course of these patients were reviewed.

Blood pressure: In all patients, preoperative ambulatory arm blood pressures were determined from hospital, office or clinical records. When multiple recordings were available, the average systolic and diastolic pressures were determined. In patients over age 18 years, hypertension was defined as resting systolic and diastolic pressures equal to or greater than 140 and 90 mm Hg, respectively. Patients under age 18 years were considered hypertensive when their systolic or diastolic blood pressure exceeded the 90th percentile for their age on at least three determinations.[51] Postoperative blood pressure was recorded at the last patient evaluation (from 1 to 28 years, mean 5.7). Patients who required chronic postoperative antihypertensive medication were included in the hypertensive group regardless of their "treated" blood pressure. Significant residual postoperative coarctation was defined by elevated arm blood pressure and simultaneous leg blood pressure at least 30 mm Hg below that in the arm. Congestive heart failure was defined by standard clinical and radiologic findings.

Associated cardiovascular disease: Because of the long interval covered by this study, management of the patients varied, and we were able to evaluate the natural history of patients in the absence of surgery as well as the effects of surgical intervention at different ages. Only patients whose "major" lesion was "adult-type" or post- or periductal aortic coarctation were included in this study.[41,52,53] Patients who had associated "simple" cardiac lesions, including patent ductus arteriosus, ventricular septal defect, and aortic or mitral valve stenosis or insufficiency, were included. Patients who had associated "severe" complex congenital heart disease, including "fetal or preductal" coarctation,[41,52,53] transposition of the great arteries, single ventricle and interrupted aortic arch, were excluded because in these patients the associated lesions were generally more important in determining clinical course and survival than the coarctation itself.

In all patients, the diagnosis of associated cardiac disease was confirmed at cardiac catheterization, surgery or postmortem evaluation. Because it was difficult to be certain of the diagnosis of associated bicuspid aortic valve retrospectively, particularly in patients evaluated during the early years of this review when clinical awareness of this condition was limited, estimation of the incidence of associated bicuspid aortic valve was not possible. Aortic stenosis was defined hemodynamically by an aortic pressure gradient greater than 20 mm Hg at catheterization or by typical postmortem findings. Aortic insufficiency was determined with clinical examination or catheterization and angiography.

Results

Age: The records of 234 patients (150 male and 84 female) with coarctation of the aorta were reviewed. At the time of definitive diagnosis, their ages ranged from 1 day to 72 years. Table I shows the age distribution of the patient population at confirmed diagnosis and the age at the time of correction of those who had surgery.

Preoperative and postoperative hypertension: Systemic hypertension was the most frequent acquired complication in these patients. Table II shows the incidence of hypertension in all 234 patients at the age of diagnosis before correction. Eighty percent of the 138 patients under age 19 years were hypertensive, and 84 percent of the 96 patients aged 19 years and older were hypertensive. Table III shows the pre- and late postoperative blood pressure in 164 of the 188 operated patients whose blood pressure was measured at follow-up (1 to 28 years [mean 5.7] after operation). In 3 of the 14 patients (21 percent) who had surgery before age 1 year, postoperative blood pressure exceeded the

TABLE I

Age at the Time of Diagnosis or Surgical Correction of Coarctation of the Aorta in 234 Patients

Age at Diagnosis (yr)	Total no. of Patients	Patients Not Operated On	Age at Time of Operation (yr) (no. = 188)*						
			<1	1–5	6–10	11–18	19–29	30–40	>40
<1	43	4†	25	10	4	...	...	...	...
1–5	24	4	...	8	10	1	1	...	...
6–10	24	4	...	...	20	...	...	...	...
11–18	47	4	...	...	...	28	10	2	3
19–29	49	11	...	...	...	2	30	5	1
30–40	23	8	...	...	...	...	1	12	2
>40	24	11	...	...	...	...	...	...	13
Total	234	46	25	18	34	31	42	19	19

* A detailed review of the surgical experience with some of these patients is now in press.[54]
† Three died with congestive heart failure and one of a cerebrovascular accident in infancy.

90th percentile for their age, and in these 3 patients the increased blood pressure was attributed to residual postoperative coarctation. Of the 17 patients who had correction between ages 1 and 5 years, postoperative blood pressure exceeded the 90th percentile in only 1 patient (6 percent); the increased pressure in this patient was related to residual postoperative coarctation.

Thirty-three patients had surgery between ages 6 and 10 years, and postoperative blood pressure in nine of these patients (27 percent) exceeded the 90th percentile for their age, although the actual pressure was greater than 140/90 mm Hg in only one patient. Residual coarctation was present in two of the nine patients. Of the 110 patients who had surgery after age 11 years, including those over age 40 years at the time of surgery, residual hypertension was present in 50 percent but was not believed to be related to persisting coarctation in any patient.

Congestive heart failure: Table IV shows the remaining acquired complications in the patient population. Congestive heart failure was most common of these complications and was present in 49 patients (17 percent). The incidence of congestive heart failure was highest in the patients under age 1 year and over age 40 years. In infancy, congestive heart failure was attributed in part to associated congenital cardiac anomalies, which were present in 29 of the 43 infants (67 percent). Congestive failure in the latter patients was refractory to medical management and required surgical intervention for the coarctation or the associated cardiac anomaly, or both. In eight of these infants, postoperative congestive heart failure persisted and was attributed to the associated anomaly in all but one infant, in whom it was secondary to residual coarctation. Congestive heart failure was present in only 4 percent of patients aged 1 to 40 years but in 67 percent of patients (16 of 24) over age 40 years. In 6 of the 16 patients with congestive heart failure who had correction after age 40 years, congestive heart failure persisted after surgery but was clinically improved, as indicated by improved symptoms, physical findings and diuretic requirements.

Other acquired complications: Cerebral vascular accidents occurred in 13 patients (6 percent); 5 of these patients had had previous repair of coarctation, but all 13 had residual hypertension. One unoperated infant, four patients aged 11 to 18 years, three patients aged 19 to 40 years and five patients older than 40 years had a cerebral vascular accident. The latter five patients comprised 21 percent of the 24 patients older than age 40 years. Bacterial endocarditis, myocardial infarction, and aortic dissection were present in five, seven and four patients, respectively.

TABLE II

Relation Between Age and Preoperative Blood Pressure in 234 Patients With Coarctation of the Aorta

Age (yr)	Total no. of Patients	Arm Blood Pressure <90th Percentile	Arm Blood Pressure ≥90th Percentile*
<1	43	12	31
1–5	24	5	19
6–10	24	4	20
11–18	47	7	40
Subtotal	138	28	110
		<140/90 mm Hg	≥140/90 mm Hg
19–29	49	7	42
30–40	23	5	18
>40	24	3	21
Subtotal	96	15	81

* According to the recommendations of the National Heart, Lung, and Blood Institute Task Force Report on Blood Pressure Control in Children.[51]

TABLE III

Relation Between Preoperative and Late Postoperative Blood Pressure and Age at the Time of Coarctation Repair in 164 Patients

Age (yr)	Total no. of Patients	Preoperative Arm Blood Pressure <90th Percentile	Preoperative Arm Blood Pressure ≥90th Percentile	Late Postoperative Arm Blood Pressure* <90th Percentile	Late Postoperative Arm Blood Pressure* ≥90th Percentile†
<1	14	2	12	11	3‖
1–5	17	3	14	16	1‡
6–10	33	5	28	24	9§
11–18	27	5	22	18	9‡
Subtotal	91	15	76	69	22 (7‡)
		<140/90 mm Hg	≥140/90 mm Hg	<140/90 mm Hg	≥140/90 mm Hg
19–29	39	5	34	19	20‡
30–40	18	3	15	11	7‡
>40	16	2	14	8	8
Subtotal	73	10	63	38	35 (2‡)

* Measured 1 to 28 years (mean 5.7) after operation.
† According to the recommendations of the National Heart, Lung, and Blood Institute Task Force Report on Blood Pressure Control in Children.[51]
One,‡, two§ or three‖ patients had residual or recurrent postoperative coarctation.

TABLE IV

Distribution of Acquired Complications in Relation to Age at Diagnosis in 234 Patients With Coarctation of the Aorta

Age at Diagnosis (yr)	Total no. of Patients at Age of Diagnosis	Congestive Heart Failure	Cerebral Vascular Accident	Bacterial Endocarditis	Myocardial Infarction	Aortic Dissection
<1	43	29 (8)	1	...	1	...
1–5	24	1	...	1 (1)	...	...
6–10	24	...	...	...	...	...
11–18	47	1	4 (3)	1 (1)	...	...
19–29	49	3	1	2	1 (1)	1
30–40	23	2	2 (1)	1	1 (1)	1 (1)
>40	24	16 (6)	5 (1)	...	4 (2)	2 (1)
Total	234	52 (14)	13 (5)	5 (2)	7 (4)	4 (2)

Numbers in parentheses indicate patients who had previously had coarctation repair.

Associated cardiac lesions: One hundred fifty-four patients had isolated coarctation of the aorta, and 80 patients (34 percent) had additional cardiac lesions (Table V). Associated congenital anomalies were present in 67 percent of our infants, most of whom had either patent ductus arteriosus, patent ductus arteriosus and ventricular septal defect, or aortic stenosis. Fifty-one (27 percent) of the 191 patients older than 1 year had associated cardiac lesions, including 18 with aortic stenosis and 9 with predominantly aortic insufficiency. In six infants, aortic stenosis was believed to contribute to congestive heart failure. At the time of this review, seven adults have had clinically significantly aortic stenosis. One of these patients underwent an aortic valve "plasty" procedure at age 18 years, four have had aortic valve replacement (at ages 28, 48, 62 and 72 years), and two patients, aged 45 and 68 years, died with unoperated severe aortic stenosis. None of our patients have required aortic valve replacement for aortic insufficiency, although one with severe aortic insufficiency is being followed up. Nineteen patients over age 1 year had associated ventricular septal defect or patent ductus arteriosus. The ductus was routinely ligated and divided at the time of coarctation repair, although this defect was not considered hemodynamically significant in any patient. No patient over age 1 year required ventricular septal defect closure.

Six patients had associated mitral valve disease, which consisted of congenital stenosis in one infant who also had aortic stenosis and rheumatic mitral disease in four adults. The latter diagnosis was made by a combination of echocardiographic findings, surgical observations and histologic study of excised valve specimens. No patient required mitral valve surgery at the time of coarctation repair.

Discussion

Hypertension and optimal age for elective surgical correction of coarctation: Hypertension is the most common and important acquired complication in patients with coarctation of the aorta, with a preoperative incidence, regardless of age, of greater than 80 percent.[7,9,15,17,27–30] Although generally well tolerated early in life, hypertension is responsible for most of the morbidity and mortality associated with coarctation with advancing age.[9,17,31–33] Thus, determination of the optimal age for surgical correction in these patients to minimize the incidence of hypertension is of paramount importance.

Attempts are now being made to define hypertension in children and to clarify its significance.[51] Although many questions remain unanswered, it appears that in the child, blood pressures lower than the standard adult hypertensive level of 140/90 mm Hg may constitute

TABLE V

Distribution of Associated Congenital Cardiac Anomalies in Relation to Age at Diagnosis in 234 Patients With Coarctation of the Aorta

Age at Diagnosis (yr)	Total no. of Patients	Isolated Coarctation	One or More Associated Cardiac Anomalies	PDA	VSD	PDA and VSD	AS	AI and AS	Mitral Valve Disease
<1	43	14*	29	13	...	13	6	...	1
1–5	24	21	3	1	...	...	...	1	1
6–10	24	19	5	3	...	...	1	1	...
11–18	47	33	14	5	...	...	6	3	...
19–29	49	39	10	4	3	...	2	1	...
30–40	23	14	9	1	2	...	2	1	3 (1)
>40	24	14	10	...	...	...	7	2	(1)
	234	154	80	27	5	13	24	9	6

* Including infants with patent foramen ovale and hemodynamically insignificant patent ductus arteriosus.
Numbers in parentheses indicate patients with mitral insufficiency.
AI = aortic insufficiency; AS = aortic stenosis; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

significant hypertension. Previous studies of postoperative hypertension in coarctation generally applied adult hypertensive criteria to children. In this study we followed the recent recommendations of the National Task Force on Blood Pressure Control in Children[51] and considered hypertension to be a level greater than the 90th percentile for the normal population of a given age group, recognizing that the long range significance of these blood pressures in children has not yet been defined.

No reported consensus now exists on the optimal age for elective coarctation repair. Numerous reports cite the increased incidence of residual coarctation when surgery is performed before age 1 year,[2,3,20,34-41] and most reports recommend delaying correction at least until after infancy.[2-11] However, one recent review[18] suggests that the optimal age for surgery should be lowered to 6 to 12 months. Our findings support the former workers[2-11] in confirming the significant incidence of residual coarctation and hypertension in postoperative infants. Furthermore, our findings clearly show that residual postoperative hypertension is not a significant problem even when surgery is delayed until age 5 years. Thus, although some infants will require emergency repair of coarctation due to congestive heart failure, it is not necessary to incur the increased risk of residual coarctation by electively correcting coarctation in the asymptomatic infant, when one can safely wait until the aorta is larger. We now delay elective correction until age 4 years. Although severe hypertension in children corrected after age 6 years is unusual, a significant number of these children have postoperative blood pressures exceeding the 90th percentile for their age; thus, delay of surgical repair beyond age 6 years should be avoided if possible.

Surgical correction in patients over age 40 years: Some workers have suggested that surgery should not be performed in older patients because of already established hypertension and the high morbidity and mortality associated with these operations.[14] In contrast, others have reported favorable postoperative results regardless of advanced age.[9,12,13,16] Our findings confirm the well known fact that the incidence of residual postoperative hypertension in coarctation increases with increasing age at the time of surgery.[2,7,9,13,15-17,24,28,29,42-44] However, 50 percent of our patients who were over age 40 years at the time of correction became normotensive, and of the 67 percent who had preoperative congestive heart failure, only 25 percent had residual failure, which even in these patients was clinically improved after operation. The only death in this group occurred in a 72 year old man during emergency simultaneous replacement of his stenotic calcific aortic valve and bypass of the coarctation, when cardiogenic shock developed during carotid endarterectomy. On the basis of these findings, we believe that although coarctation repair carries a higher risk and offers less dramatic improvement in older patients, repair should not be denied these patients on the basis of age, long-standing hypertension or even congestive heart failure.

Management of congestive heart failure: After hypertension, congestive heart failure was the most common acquired complication in our patients. The distribution of congestive heart failure was bimodal; it occurred in two-thirds of our infants and in two-thirds of our patients over age 40 years. In the infants, congestive heart failure was most often related, at least in part, to associated congenital heart lesions; in the adults it was generally attributed to chronic hypertension and occasionally to aortic valve disease. In contrast, congestive heart failure was rare in patients aged 1 to 40 years.

Management of the infant with medically refractory congestive heart failure presents a difficult problem that is often related more to the surgical management of the associated cardiac anomalies than to the coarctation itself.[3,4,8,9,17-29] Although an associated patent ductus arteriosus is readily ligated at the time of coarctation repair, in infants with a large ventricular septal defect or aortic stenosis both medical and surgical mortality are high, as indicated by our own experience and as reported by others.[8,45] Conversely, when refractory congestive failure is due to isolated coarctation of the aorta, the results of emergency surgery performed in infancy are excellent.

Management of associated cardiac lesions: Infants who present with coarctation have a high incidence of associated congenital cardiac lesions that often require intervention; in contrast, in patients older than age 1 year, clinically significant associated cardiac lesions are less common and rarely require additional surgery. Although bicuspid aortic valve is commonly associated with coarctation,[8,16,17,23,25,27,28,32,33,46,47,49] the clinical significance of this association has received little attention. Fourteen percent of our patients had documented aortic stenosis or insufficiency. When identified during infancy, associated aortic stenosis was often severe and contributed significantly to early failure. After infancy, clinically severe aortic valve disease was uncommon and rarely necessitated aortic valve surgery until late in life. However, with the increased longevity made possible by early coarctation repair, significant aortic valve disease will undoubtedly become more frequent in such patients.

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Toxoplasmic Infection in Cardiac Disease

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In 18 patients who presented in less than 2 years with heart disease characterized by arrhythmias (including atrial fibrillation, ventricular arrhythmias and heart block), atypical chest pain, pericarditis and cardiac failure, extensive investigation revealed no cause for the disease except for evidence of toxoplasmic infection. One patient had acute toxoplasmosis; the other 17 patients had chronically increased titers, higher than the expected level in the community and also higher than in a control series of patients with well defined heart disease. Toxoplasmosis is probably a fairly common cause of heart disease in this community. The source of infection appeared to be cats, uncooked meat and congenital infection. Patients received chemotherapy with either pyrimethamine and sulfadiazine or tetracycline. Serious relapse occurred in three patients and embolic complications in two. Experimental myocarditis occurs when toxoplasmic cysts rupture within the heart; therefore clinical symptoms may occur sporadically during a chronic infection.

Infection with Toxoplasma gondii is common in both animals and human beings throughout the world. In contrast, the recognition of clinically significant disease is relatively uncommon, except in the case of congenital intra-uterine infection, which may cause stillbirth or severe neonatal illness and death from meningoencephalitis and myocarditis. In adults, acquired toxoplasmosis has three forms: first, the miliary infection with widespread organ involvement pursuing a severe course; second, the glandular type that involves only the lymph nodes and runs a benign course resembling infectious mononucleosis[1]; and, finally, the localized type with involvement of only one or two organs. This group includes toxoplasmic myocarditis,[2] hepatitis,[3] chorioretinitis,[4] polymyositis[5] and glomerulonephritis,[6] as well as various neurologic disorders including meningoencephalitis and single and multiple mass lesions.[7]

Toxoplasmic myocarditis is considered a rare disease; however, our experience over the last 2 years indicates that in a relatively well defined group of patients with recurrent arrhythmia, atypical chest pain and chronic congestive heart failure extensive investigation reveals no cause of disease except for the presence of chronic or latent toxoplasmic infection. If this relation is direct, then toxoplasmic myocarditis is a fairly common cause of heart disease in urban North America. Our experience with 18 patients with toxoplasmic myocarditis is presented.

Patients

Eighteen patients who were referred for diagnosis and treatment of cardiac arrhythmias, chest pain or heart failure are presented. All were studied initially for evidence of the common forms of heart disease (including coronary, hypertensive, valvular, congenital, alcoholic, infective and thyrotoxic heart disease) using the standard techniques of history and physical examination, 12 lead electrocardiography, chest X-ray film, echocardiography and when appropriate, serum thyroxine, serial viral antibodies, exercise test (supine bicycle ergometer

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or treadmill), cardiac catheterization and coronary angiography. As a result of these investigations, a cardiomyopathy was suspected in the 18 cases and toxoplasmosis was considered. The retinas were examined and direct inquiry into dietary history for ingestion of raw or rarely cooked meats, and exposure to cats was made. The patients' occupational history was reviewed for exposure to farm animals, including goats, and to animal flesh.

Serial toxoplasmic antibodies were studied over a 2 year period and were measured by the serology laboratory, Ministry of Health of the Province of Ontario, Toronto, for the toxoplasmic indirect fluorescent antibody (IFA) test and by the Toxoplasmosis Diagnostic Laboratory, Ontario Veterinary College, University of Guelph, for the Sabin-Feldman dye (SFD) test.

The severely ill patients were nursed in the acute cardiac care unit with continuous electrocardiographic monitoring and standard cardiac intensive care. Patients were treated with digoxin, diuretic drugs, electrolyte supplementation and antiarrhythmic drugs as required. Nine patients were treated for toxoplasmosis with pyrimethamine (Daraprim®), 50 mg daily, and sulfadiazine, 0.5 g 4 times a day. In these patients, hemoglobin determination, white blood count and platelet count were performed at least twice a week. Leukopenia and thrombocytopenia or gastrointestinal complications such as glossitis or esophagitis were treated with folinic acid (calcium leucovorin), 9 mg intramuscularly, for 3 days. The remaining nine patients were treated with tetracycline, 500 mg 4 times a day for 4 weeks, and several patients had repeat courses of chemotherapy with tetracycline. All patients were followed up from diagnosis, clinical relapses were noted, and further treatment was given as appropriate.

The toxoplasmic antibodies of the patients' relatives living at home, and in some cases of their domestic animals, were also studied. A single test to determine the titer of antibodies was also performed in a control series of 44 patients of a similar age group with well defined heart disease including rheumatic, ischemic and congenital heart disease.

Results

Clinical features: The age, sex, presenting features and the presence of heart failure, atrial or ventricular arrhythmia and chest pain are included in Table I. The patients included 12 men and 6 women. Only four patients were over age 60 years and four were under age 40. Heart failure was the presenting feature in four patients. Three other patients had exertional dyspnea without overt failure. Six patients had atypical chest pain, which was the chief presenting complaint in two patients. Two patients had acute pericarditis. Eight patients presented with palpitations and one with syncope and dizziness, probably due to Stokes-Adams attacks. Thirteen patients had atrial arrhythmias and three had ventricular arrhythmias. One patient had first and second degree heart block (Mobitz I) as well as atrial tachycardia and atrial fibrillation. Another patient had paroxysmal second degree heart block (Mobitz I). Retinal examination revealed evidence of toxo-

TABLE I

Presenting Complaint and Clinical Features of Heart Disease

Case no.	Age (yr) & Sex	Duration of Symptoms	Heart Failure	Arrhythmias	Chest Pain
Acute Toxoplasmosis					
Severe heart failure					
1	56 M	1 wk	Biventricular	Ventricular bigeminy, atrial fibrillation	Atypical
Chronic Toxoplasmosis					
Heart failure					
2	63 M	6 yr	Left ventricular	Atrial fibrillation	Atypical
3	44 F	5 yr	Left ventricular	Atrial fibrillation	Atypical
4	58 M	3 yr	Left ventricular	Atrial fibrillation	. . .
Chest pain					
5	28 M	3 mo	. . .	. . .	Atypical
6	41 M	12 yr	. . .	Parox 2nd degree A-V block	Atypical
7	52 M	1 hr	. . .	. . .	Acute pericarditis
8	41 M	1 day	. . .	. . .	Acute pericarditis
Arrhythmias					
9	26 F	6 yr	. . .	20–30 ventricular ectopic beats/min	. . .
10	30 F	3 mo	. . .	Parox atrial tachycardia and fibrillation; 2nd degree A-V block	. . .
11	40 M	2 mo	. . .	Parox atrial fibrillation	. . .
12	36 F	7 yr	. . .	Recurrent supraventricular tachycardia	. . .
13	46 M	3 hr	. . .	Parox atrial fibrillation	Atypical
14	83 F	7 yr	. . .	Atrial fibrillation	. . .
15	62 M	1 yr	. . .	Atrial fibrillation; ventricular ectopic beats	. . .
16	63 M	5 yr	. . .	Atrial fibrillation	. . .
17	48 F	5 wk	. . .	Parox atrial flutter	. . .
Cerebral embolism					
18	53 M	7 mo	. . .	Parox atrial fibrillation	. . .

A-V = atrioventricular; parox = paroxysmal.

plasmic involvement in only one patient (Case 12), who had been blind in the left eye since age 2 years as a result of toxoplasmic choroiditis.

Viral and toxoplasmic antibody studies: Serial examination for viral antibodies was performed in five patients (Cases 1, 7, 8, 13 and 17) with a recent sudden onset of symptoms. The groups tested included Coxsackie B_2, B_3, B_4 and B_5; influenza A/Victoria, A/Swine, A/Port Chalmers and also Para-influenza 1, 2 and 3 viruses. Patient 9, when pregnant, was studied for rubella, cytomegalovirus and hepatitis B. No titer increased significantly in any of these patients.

The results of serial toxoplasmic antibody tests (Table II) indicate that the infection was chronic in all patients except one (Case 1). This patient had a negative titer in 1970, and in 1976 presented with severe acute heart failure with a high titer that was apparently decreasing even before chemotherapy was given; after treatment, he had a fairly stable chronically positive titer. In general, the Sabin-Feldman dye (SFD) test and indirect fluorescent antibody (IFA) test showed fairly close agreement and either the SFD or the IFA test were 1:256 or greater in all, except in one patient (Case 10) at 1:128.

TABLE II

Serial Toxoplasmic Antibody Tests and Chemotherapy

Case no.	Tests 1	2	3	4	5	6	7	8	9	10	11	12	Follow-up (mo)
Acute Toxoplasmosis													
1	Neg (1970)	> 1024 4096 (1976)	1024 1024*	256	64	256 256	256 256	256 256	64†	64	256	256	24
Chronic Toxoplasmosis													
2	1024 1024	1024 1024†	256	256	256	256							16
3	1024 256	1024 256†	1024 256	256	256	256	256						16
4	256	256 64†	256	256	256								12
5	1024 256	1024 256*	256	256	256								21
6	128 256	64 256	128 256*	64†	64	64	64	64					22
7	256 256	256 256	256 256*	256 256	256 256	256							20
8	256	256†	256	256	256								9
9	256 64	1024 64*	1024 64	256	256								17
10	128 64	128 64*	128 64	256 16†	128 16	128 16†	64	64					17
11	1024 256	1024 256*	1024 256	256	256								17
12	64 256	256 256*	256 256	256 256	256	256							17
13	256 256	256 256†	64	64									13
14	1024 1024	1024 1024†	1024 1024	1024 1024									17
15	256	64†	64	64									12
16	256	256†	256										3
17	256	256†	256										3
18	256 256*	256 64	256 64	64									24

* The patient received chemotherapy with pyrimethamine and sulfadiazine after this test.
† The patient received chemotherapy with tetracycline after this test.
All dilutions are expressed as whole numbers; for example, 256 indicates a dilution of 1:256.
For each patient, the first row represents the antibody titer determined with the Sabin-Feldman dye test, and the second row represents the titer with the indirect fluorescent antibody test.
Neg = negative.

Cardiac diagnostic procedures: The electrocardiogram was normal in only two patients. Fifteen patients had arrhythmias and one patient had a hypertrophic pattern. Three patients had saddleback S-T elevations, suggestive of pericarditis, and one patient had diffuse T wave inversion in the anterior and inferior leads. The chest X-ray film was normal in eight patients; eight patients had cardiomegaly and three had pulmonary congestion or edema. Two patients had pleural effusions. Echocardiography was performed in 17 patients; the results were normal in 9. Right ventricular dimensions were increased in two patients, left atrial dimensions were increased in five, and left ventricular diastolic dimensions were increased in two patients. One patient had paradoxical septal motion.

Five patients underwent exercise testing before the diagnosis of toxoplasmosis was established. Only one patient achieved the maximal predicted work output. One patient (Case 6) had frequent ventricular ectopic complexes after exercise, and Patient 9 had frequent ventricular ectopic complexes both before and during exercise. These patients, therefore, demonstrate exercise intolerance and ventricular irritability.

Cardiac catheterization and coronary angiography in Patients 2 and 6 disclosed evidence of diffuse left ventricular hypokinesia and dilatation in Patient 2 and a normal left ventriculogram in Patient 6. No significant coronary artery disease was evident in either patient.

Modes of infection: Possible modes of infection and the results of antibody tests in close relatives are presented in Table III; only one patient (Case 10) had no exposure to pets or farm animals, disliked rare meat and had family members with negative antibody test results. The mode of infection in this patient is unknown, but as a housewife, she was probably exposed to uncooked meat. One patient (Case 1), a realtor, cleaned up an old farm house filled with animal excreta and dust just 2 weeks before the onset of heart failure associated with a very high antibody titer. Titers had been negative several years earlier.

Six patients had cats. In one patient's family, both the cat and the dog had positive titers. This patient's

TABLE III

Possible Mode of Infection and Family Infection

Case no.	Duration of Symptoms	Duration of Exposure	Mode of Infection	Close Relatives
			Acute Toxoplasmosis	
1	1 wk	2 wk	Cleaned old infested farmhouse	W neg
			Chronic Toxoplasmosis	
2	6 yr	Chronic	Meat renderer	W, 1C neg
3	5 yr	7 yr earlier	Cat died 7 yr earlier	Refused
4	3 yr	Chronic	Raw meat; farm laborer before 1956	W neg
5	3 mo	Chronic	Goat's meat	Single
6	12 yr	Chronic	Goat farm exposure	W, 3 C neg
7	1 hr	Chronic	Uncooked hamburger sandwiches; cat 1:256; dog 1:256	W 1:1024 2 C neg
8	1 day	Chronic	Goat's meat	W 1:64 3 C neg
9	6 yr	Chronic	Uncooked beef tartare and pork sausage; cat	H 1:128
10	3 mo		No pets; no uncooked meat	H, 1 C neg
11	2 mo	Chronic	Raw sausage	M 1:1024 (Case 14)
12	7 yr	In utero	Mother infected during pregnancy	H, 1 C neg
13	3 hr	Chronic	Cat	W, 3 C neg
14	7 yr	Chronic	Raw sausage	C = 1:1024 (Case 11)
15	1 yr	Chronic	Cat	W, 2 C neg
16	5 yr	Chronic	Butcher	W neg
17	5 wk	Chronic	Cat	H, 3 C neg
18	7 mo	Chronic	Rare meat	Refused

C = child or children; H = husband; M = mother; neg = negative; W = wife.

wife had a titer of 1:1024 and was the only relative with such a high titer who had no sign of heart disease. One patient had had an ill cat destroyed 7 years before the study; cardiac symptoms developed 2 years later. *Six patients liked uncooked or rare meat and meat products* including beef tartare, uncooked hamburgers and uncooked pork sausage; four of these patients had relatives with positive titers. Two patients liked goat's meat, and the wife of one of them had a positive titer (1:64). Another patient had been to a goat farm and had drunk goat's milk. One patient had worked for 13 years at a meat rendering company that processed old unused meat and meat products. Four years before the study, he had retired with a disability pension for heart failure due to cardiomyopathy. His close relatives had negative titers. Another patient was a butcher. Patient 12 is unusual in this group because she probably acquired infection in utero. She had choroiditis at age 2 years and nephritis at age 8 years. There was no exposure to pets, farm animals or uncooked meats, and both her husband and child had negative antibody tests.

Of the 18 patients, therefore, 16 had chronic or long-term previous exposure, and only 1 patient (Case 1) had recent exposure that resulted in acute toxoplasmosis. As indicated in Table III, a patient's symptoms may be acute and recent despite evidence of only chronic infection.

Treatment: All patients received appropriate treatment with digoxin, diuretic drugs and electrolyte supplementation for heart failure and with digoxin and propranolol if necessary for arrhythmias; two patients with cerebral embolism (Cases 1 and 18) were treated with anticoagulant drugs. All patients' initial symptoms and signs were controlled in this manner. In an effort to prevent further relapses, they also received a course of chemotherapy (Table II). Nine patients received pyrimethamine and sulfadiazine. The patient with acute toxoplasmosis (Case 1) had a sustained decrease in titer, although the titer remained chronically positive. Of the eight patients with chronic infection, only patient 6 had a permanent decrease in titer to 1:64. A consistent decrease in titer occurred in two of nine patients receiving tetracycline (Cases 2 and 13).

Relapses: Three patients had serious relapses after treatment. One year after control of symptoms and chemotherapy with pyrimethamine and sulfadiazine, severe heart failure with atrial fibrillation developed in Patient 1 at a time when the antibody titers were low. He was given a course of tetracycline and his condition remitted. Four months later, he had two episodes of cerebral embolism; he was treated with anticoagulant drugs and recovered. Patient 6 had a further episode of severe atypical chest pain, complicated by transitory second degree (Mobitz I) atrioventricular block, 8 months after chemotherapy when his antibody titer had decreased (Table II). There was no clinical, electrocardiographic or echocardiographic evidence of pericarditis or myocardial ischemia. Coronary angiograms and left ventriculograms were normal. He was given a course of tetracycline, and no further episodes occurred. Patient 10 had a further episode of second degree atrioventricular block with syncope 8 months after chemotherapy at a time when the SFD titer was increased. She received a course of tetracycline therapy after this, but had a further attack 3 months later. The remaining patients did well and had no further relapses.

Complications of therapy: These occurred in several patients. Leukopenia and thrombocytopenia developed in four patients receiving pyrimethamine. They were treated with folinic acid, 9 mg intramuscularly for 3 days, and were able to continue chemotherapy. Gastrointestinal side effects occurred in two patients: glossitis in one, and esophagitis in another; both patients responded to treatment with folinic acid. As a result of this experience, patients receiving pyrimethamine were also given folic acid, 5 mg twice daily by mouth, and no further complications occurred. One patient was unable to tolerate the nausea and anorexia that were common in the patients receiving pyrimethamine; she and eight other patients (one of whom had thrombocytopenia before treatment) were treated with tetracycline, 500 mg four times daily for 1 month, without ill effect.

Control series: In the control series of 44 patients with an average age of 41 years, collected from the same referral population, 8 patients (18.1 percent) had a low positive titer. The highest was 1.64.

Discussion

Significance of Toxoplasmic Antibody Titers in Clinical Diagnosis

Establishing a causal relation between evidence of toxoplasmic infection and myocarditis is difficult. Even at autopsy, the evidence may be only indirect and, like the clinical evidence, based largely on a process of exclusion. The reasons for this are both epidemiologic and pathologic. Many communities have a large prevalence of toxoplasmic infection but a small incidence of clinical manifestations. Parallel pathologic data demonstrate that myocardial involvement with toxoplasma does not necessarily lead to myocarditis. When low positive toxoplasmic antibody titers are common in a community, assessment of the significance of a positive titer requires some knowledge of the local prevalence rate. The incidence rate of low positive titers in some cities in Canada and the United States is as follows: Toronto, 25 percent[8]; Montreal, 26 percent[9]; Syracuse, 30 percent[10]; and Pittsburgh, 35 percent.[11] Therefore, low level titers are common. Higher titers are much less frequent: for example, in Montreal, of 1,516 sera examined, only 8 percent had a titer of 1:256 or greater, many with clinical toxoplasmosis, and in Toronto, 6 percent had a titer of 1:256 or greater. It is generally agreed that a level of 1:256 is clinically significant and represents active or past infection.[9,12-14] In acute disseminated toxoplasmosis, often complicating immunosuppressive chemotherapy, and in glandular toxoplasmosis, the levels are much higher and serologic diagnosis is not difficult.

In chronic retinitis and myocarditis the situation is different. In ocular cases, titers as low as 1:64[15] are considered significant. In isolated myocarditis some authors[16,17] have accepted levels as low as 1:16 or 1:64,

and an SFD titer of 1:32 was found in a fatal case of toxoplasmic myocarditis that was confirmed at autopsy.[18] In view of the prevalence rates of low titers such as 1:16 and 1:64 in the border areas of eastern Canada and in the United States, a level of 1:256 is probably required to suggest the diagnosis of toxoplasmic myocarditis in most cases. Occasionally, if the clinical evidence for the diagnosis is strong and other causes can be excluded, a titer of 1:128 may be acceptable. In our control series of 44 patients with known heart disease, 18 percent had a low positive titer to a level of 1:64, which is comparable with the level found in other general population studies from this area[8,9] and differentiates patients with known heart disease from our group of patients with toxoplasmosis and a high stable titer of toxoplasmic antibodies.

Chronic or Latent Toxoplasmic Infection and Myocarditis

Under what conditions may a chronic or latent toxoplasmic infection lead to myocarditis? This depends on the life cycle of the toxoplasmic parasite. After infection through the human gastrointestinal tract, a parasitemia develops and the organism is widely distributed in the invasive trophozoite form.[19] In the heart, the trophozoite invades myocardial cells, leading to cell death. In an acute miliary infection or a congenital infection, acute myocarditis develops with focal myocardial necrosis and infiltration with histiocytes, lymphocytes and plasma cells.[16] This process does not occur in most adults; instead, the trophozoite matures to the encysted stage and probably remains viable in the myocardium throughout life.[10] It is probably from this chronic latent infection that local myocarditis may develop if a cyst ruptures. Pathologic data are available in only a few cases of localized myocarditis. Most of these cases demonstrate a nonspecific diffuse interstitial fibrosis, but toxoplasma was isolated by animal inoculation in some of these cases.[16,18,20] Animal experiments confirm the importance of cyst rupture, indicating that typical electrocardiographic abnormalities do not occur with pseudocyst formation but occur only when diffuse myocarditis develops after rupture of a cyst.[21] The degree of virulence of the strain of toxoplasma may also be important; for example, in the rabbit, histologic myocarditis was much more frequent with low than with high virulence strains (96 percent compared with 31 percent), and more severe electrocardiographic abnormalities (including ventricular extrasystoles and conduction disturbances) occurred. The electrocardiographic abnormalities occurred at a later stage in the infection, when recovery of the parasite from the myocardium was less likely and some healing by fibrosis had occurred.[22] An interesting parallel was demonstrated in man by the isolation of an organism of low virulence from the lymph node of a patient with glandular toxoplasmosis and myocarditis and many ventricular extrasystoles.[23]

Judged from these data, it appears likely that clinical myocarditis develops at a late stage of the infection, probably with a strain of toxoplasma of low virulence, at a time when some healing has occurred. Our serologic data strongly support this view and demonstrate that in all but one case clinical myocarditis developed and exacerbations occurred during the late or chronic phase of infection. Epidemiologic data from this area[24] collected by the Ontario Veterinary College (Guelph) demonstrate a marked cyclical pattern of serologic evidence of human infection with peaks in 1962, 1967 and 1973; therefore, our cases were collected in years when the prevalence rate was low. This again suggests a relation to chronic and latent infection. Therefore, experimental, serologic and epidemiologic data demonstrate that local myocarditis occurs most frequently during the chronic phase of toxoplasmic infection.

Toxoplasmic Myocarditis

The clinical features of this type of myocarditis are fairly consistent and lead us to suggest that a definite and not uncommon clinical entity exists that is characterized by arryhthmias, particularly atrial fibrillation, precordial discomfort and heart failure.

Arrhythmias: The majority of our 18 patients had significant arrhythmias; 13 patients had atrial arrhythmias, 3 had ventricular arrhythmias and 2 had conduction disturbances. One patient had paroxysmal supraventricular tachycardia, one had paroxysmal atrial flutter, four had paroxysmal atrial fibrillation and seven had long-standing atrial fibrillation. Two patients had paroxysmal second degree atrioventricular (A-V) block (Mobitz type I); one of these patients had syncopal attacks and episodes of supraventricular tachycardia and paroxysmal atrial fibrillation, suggesting both A-V nodal and atrial disease. Increased ventricular irritability is an important feature of toxoplasmosis, and frequent ventricular ectopic complexes (up to 30/min) were found in three of our patients.

Previous isolated case reports of toxoplasmic myocarditis described a variety of supraventricular arrhythmias, including supraventricular tachycardia,[25] nodal rhythm,[2] atrial flutter[26] and atrial fibrillation[27]; conduction disturbances, including first degree A-V block,[16] second degree A-V block with Stokes-Adams attacks[28] and bundle branch block[18]; and ventricular arrhythmias, including ventricular tachycardia with syncopal attacks[29] and frequent premature complexes.[16] Thus, arrhythmias occur frequently in toxoplasmic myocarditis, and atrial fibrillation, either paroxysmal or long-standing, is apparently the most characteristic. In fact, when atrial fibrillation occurs in a middle-aged patient and the common forms of heart disease such as coronary, hypertensive and valvular heart disease can be excluded, toxoplasmosis should be seriously considered. It should also be considered when conduction disturbances occur at an early age.

Embolic phenomena: Several reports have described embolic complications of toxoplasmic myocarditis.[16,20,27] In our series, two patients had episodes of transient cerebral ischemia; one episode was associated with paroxysmal atrial fibrillation and the other occurred 3 months after the onset of permanent atrial fibrillation. Both patients were treated with oral anticoagulant therapy and have had no recurrence. Embolic complications are probably fairly common in toxo-

plasmic myocarditis because of the frequency of atrial fibrillation and the occurrence of left atrial dilatation, as noted in several of the echocardiograms.

Atypical chest pain and pericarditis: Atypical chest pain with precordial heaviness is mentioned in several reports of toxoplasmic myocarditis.[16,17] Six of our patients had similar symptoms, and in two patients atypical chest pain was the presenting complaint. In some of these six patients, the pain may have been pericardial in origin. For example, one patient had several attacks of severe chest pain over 12 years that had been suspected but not proved to be caused by pericarditis; coronary angiograms were normal. In addition, two of our patients had typical acute pericarditis with a loud friction rub. Viral screening tests for other causes of pericarditis in both patients were negative, and the home environment of both showed evidence of toxoplasmic infection. An editorial review in 1969 indicated that only five cases of toxoplasmic pericarditis had been reported.[17] The pericarditis was part of an acute toxoplasmosis with high antibody titers in all five patients, whereas the toxoplasmic infection was chronic in both of our patients.

Heart failure: Mild to moderate heart failure, often described as a chronic cardiomyopathy,[16,17] is a fairly common symptom, and it occurred in three of our patients. Cardiac catheterization disclosed left ventricular dilatation with generalized hypokinesia without evidence of significant coronary or valvular heart disease. In contrast, our only patient with acute toxoplasmosis had rapidly progressive heart failure, a presentation similar to that in the previously described case of a 30 year old policeman who died within 2 months of the onset of symptoms.[18] Therefore, although toxoplasmic myocarditis usually presents as chronic congestive cardiac failure, it can also cause rapidly progressive and even fatal heart failure.

Aids to diagnosis: The diagnosis of toxoplasmic myocarditis requires the exclusion of other specific forms of heart disease and the establishment of evidence of toxoplasmosis with serologic testing. There are three groups of antibodies[30] in which the timing of peak titers differs: the IgM-IFA antibody, in which the peak titer occurs early; the cell wall antibody (SFD, CF and IFA tests), in which it is intermediate, and the antibody to soluble internal antigen (IH test), in which it is late. The examination of one sample for all three groups should determine the timing of the infection. In practice, many of these tests are not available (as in our series), and most data are acquired from serial SFD and IFA tests, whose results are generally in close agreement.[31,32] Our data demonstrate that in most cases, evidence of a chronic infection will be established.

Cardiac investigations demonstrate that the electrocardiogram is rarely normal in these patients; it was normal in only 2 of our 18 patients. The chest X-ray film may show cardiomegaly or pulmonary congestion, but in half of our patients it was normal. Although the echocardiogram may disclose chamber enlargement and dilatation, particularly in patients with heart failure, in our patients with arrhythmia only, it was usually normal.

Several patients underwent exercise testing before the diagnosis was established. Only one patient achieved his predicted work output. In one young patient, marked ventricular ectopic activity was not decreased by exercise, and in another patient, frequent multiple ventricular extrasystoles occurred just after exercise. Exercise testing is hazardous in patients with toxoplasmic myocarditis because of the frequency of arrhythmias at rest and the chance of increased ventricular irritability during the test.

Cardiac catheterization is seldom indicated, provided the diagnosis of cardiomyopathy can be established with other methods. Coronary angiography may be required occasionally to clarify the nature of chest pain.

Mode of Infection

How is the infection acquired in the adult? The life cycle of toxoplasma gondii is completed in the cat, which is the only animal that contains the oocyst, which is excreted in the feces.[33] Infective oocysts are found in the soil; snails, earthworms, flies and cockroaches may act as vectors.[34] As a result, many farm animals become infected when grazing and act as intermediate hosts. In southern Ontario, 40 percent of the cattle and pigs, 88 percent of the sheep and 96 percent of the goats have positive titers.[24] Therefore infected meat is probably an important source of infection in humans. Because the parasite is killed by heat, uncooked and rarely cooked meat and sausage, such as beef tartare, are an obvious source of infection. Unpasteurized milk, particularly goat's milk, may also be infected.[35] However, exposure to cats is probably a more common source of infection than meat eating or congenital spread.[36,37]

Our 18 cases confirmed these common modes of infection. Six patients had cats. Ten patients had been exposed to uncooked meat; one of these patients was employed as a butcher and another as a meat renderer. High levels of antibodies were previously described in slaughterhouse workers.[38] Six patients liked uncooked meat, two liked goat's meat, and one drank goat's milk. Obtaining a careful dietary history in patients with unusual forms of heart disease was a useful method of initiating the diagnosis. Two rarer sources of infection were cleaning an old farmhouse and infection in utero. A previous review of sources of infection of adult toxoplasmic myocarditis revealed no other cases of relapsed intrauterine infection.[17]

Rarer sources of infection in humans include laboratory accidents[39] and possibly renal transplantation.[40] A transitory increase in antibody titers may also sometimes follow blood transfusions,[34] possibly because of a passive transfer of antibodies.[41] Passive transfer of antibodies occurred in utero in one of our patients.

Toxoplasmosis has been described frequently in patients receiving immunosuppressive therapy, especially in malignant disease[42] and, more rarely, after renal transplantation.[40] In many of these patients, the disease is generalized, difficult to diagnose and frequently dominated by involvement of the central nervous system. Reviews of the cerebral forms of toxoplasmosis demonstrate that most of the patients received immunosuppressive therapy, whereas none of our

patients with toxoplasmic myocarditis had received such treatment.

Prognosis and Mortality

The overall prognosis of toxoplasmic myocarditis is not well known. However, a number of fatal cases were reported in young people. In one series of 11 cases collected in 6 years in Chile,[16] three patients died at ages 17, 43 and 44 years, respectively. Other fatal cases include a 20 year old woman,[27] a 36 year old woman,[43] two men, aged 29 and 30 years[20] and a 30 year old man.[18] It would be premature to indicate a mortality rate for toxoplasmic myocarditis, but the reported deaths suggest that it is probably quite high. This relatively poor prognosis is emphasized by the serious symptomatic relapses that occurred in 3 of our 18 patients despite chemotherapy. These relapses included heart failure and two episodes of conduction disturbances. However, in another group of patients, who often present with supraventricular arrhythmias, including paroxysmal and chronic atrial fibrillation, the prognosis is probably good unless embolic complications are present. It is not clear whether the condition of such patients can become more serious at some stage and run a more malignant course or whether treatment will prevent this.

Treatment

Sulfadiazine-pyrimethamine: In acute infections in animals, both sulfadiazine[44] and pyrimethamine (Daraprim®)[45] are effective and interact synergistically with an 8-fold increase in activity.[46] Unfortunately, in chronically infected animals, a radical cure is often not obtained[47] because the drugs are effective only against multiplying organisms.[48] The disadvantages of this therapy are considerable because pyrimethamine, which is a folinic acid antagonist, must be administered in large doses that are almost toxic. Leukopenia, thrombocytopenia, glossitis and esophagitis are frequent complications that respond to folinic acid and may be prevented by administering folic acid throughout treatment. A search for alternative, more tolerable therapy has included tests of trimethoprim-sulfur combinations that were successful in both experimental[49] and human[50] toxoplasmosis but less effective than the pyrimethamine-sulfadiazine combination, at least in the immunocompromised patient.[51]

Tetracyclines: Tetracyclines were also tested. Dimethylchlortetracycline was successful in experimental toxoplasmosis[52]; in clinical studies, oxytetracycline caused two clinical remissions in a patient with glandular toxoplasmosis that was resistant to pyrimethamine-sulfadiazine.[53] The confirmation of tetracycline as effective therapy would constitute considerable progress because this agent is much less toxic than pyrimethamine-sulfadiazine. We used tetracycline in nine patients with toxoplasmic myocarditis, including one patient with thrombocytopenia. A decrease in titer occurred in two patients; heart failure lessened in one patient, and the other has had no relapse of atrial fibrillation.

As demonstrated in this study, toxoplasmic myocarditis is usually associated with evidence of chronic infection. Therefore, results of treatment may be disappointing. Of 11 patients treated in one series, the condition of 8 improved, but 3 died with progressive myocarditis.[16] Three other patients died after short-term administration of pyrimethamine and sulfadiazine.[18,20]

Relapses: Our results demonstrate that patients with toxoplasmic myocarditis have a potentially poor and unpredictable prognosis, with serious relapses occurring after chemotherapy. The relapses are not related to the antibody titer and may occur at times of stable, increasing or decreasing titers. The effect of chemotherapy on antibody titers is not consistent, and treatment with pyrimethamine and sulfadiazine is unpleasant, prone to complications and apparently not superior to treatment with tetracycline. In patients who had a relapse, a further course of treatment with tetracycline was given, but further relapses still occurred. These patients may benefit from long-term chemotherapy, as is required in other chronic infections with a fibrotic response. Other workers[16,17,28] recommended the short-term use of steroids in addition to specific therapy in treating toxoplasmic myocarditis, on the grounds that it will suppress inflammation and perhaps reduce necrotic lesions that may be autoimmune phenomena and that it also may improve impaired conduction. We have had good short-term results without steroids. However, no definite method of preventing the chronic relapsing nature of the disease is now apparent; in this respect the disease shows interesting parallels with Chagas' disease, in which evidence of myocarditis persists long after the initial infection with South American trypanosomiasis and the parasite is equally difficult to recover from the myocardium.

Prevention: The present treatment for toxoplasmic myocarditis is unsatisfactory, and alternative methods of managing the disease are needed. Some progress toward the development of a safe vaccine has been made, and it has been suggested that the vaccine could be used to protect nonimmune women in high risk areas and patients on immunosuppressive therapy.[54] In the home, improved cleanliness with cat litter, careful hand washing after handling uncooked meats and more thorough cooking of meat would reduce exposure to infection. Prevention of disease in the cat, both in the home and on the farm, with some form of vaccination is probably the most direct method of prevention.

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Echocardiographic Manifestations of Persistence of the Right Sinus Venosus Valve

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The echocardiographic features of a neonate born with a persistent right sinus venosus valve are presented. Because surgical correction of this serious anomaly may be possible, the diagnosis should be made soon after birth. An echocardiogram suggesting a right atrial myxoma, an unlikely finding in a neonate, should be an important clue to the diagnosis of this anomaly.

Congenital anomalies of the valve of the sinus venosus are extremely rare.[1-4] We observed in a newborn girl with this anomaly all the clinical features of severe obstruction of the outflow tract of the right ventricle. The rarity of the anomaly, coupled with its peculiar echocardiographic manifestations, prompted the publication of this report.

Case Report

An infant girl was referred at age 24 hours because of cyanosis associated with a cardiac murmur heard immediately after birth. Gestation and delivery had been uneventful. The Apgar score was 3 at 1 minute and 6 at 5 minutes. On examination, no cardiorespiratory distress was noted. The infant had normal color at rest, but cyanosis was noted after feeding or during crying. She weighed 2.7 kg. The respiratory and heart rates were 40 and 150/min, respectively. A grade 3/6 systolic ejection murmur heard along the left sternal border was maximal at the second left intercostal space and radiated to the back. No murmur was heard during diastole. An electrocardiogram suggested right ventricular hypertrophy. The chest roentgenogram (Fig. 1) showed marked cardiomegaly with an upturned apex, compatible with enlargement of the right ventricle, and a prominent right border suggesting a dilated right atrium. Lung vascularity was decreased. A clinical diagnosis of either Ebstein's anomaly or pulmonary atresia with intact ventricular septum was made.

Echocardiographic findings: An echocardiogram was taken with an Ekoline 20A ultrasonoscope coupled with a Cambridge fiberoptic recorder. A 5 megahertz unfocused transducer was used. When the transducer was positioned at the fourth left intercostal space, a cloud of echoes was visible in diastole, close to the tricuspid valve and moving into the right ventricular cavity (Fig. 2). In the sweep toward the aorta, these echoes could be followed up to the right ventricular outflow chamber (Fig. 3). They were clearly separated from the tricuspid valve itself, which had normal motility with a normal E-F slope. The time of closure of the tricuspid valve was not abnormally delayed over that of the mitral valve. During ventricular systole, these additional echoes disappeared. Septal motion and the mitral valve appeared normal, as did the volume of the right and left ventricular cavities. This echocardiogram led to the diagnosis of a tumor mass thought to be probably located in the right atrium at the level of the tricuspid valve and entering into the right ventricle during diastole.

Hemodynamic and angiographic studies: These were carried out the next day and showed no tumor mass but a spinnaker-like image bulging back into the right atrial cavity during systole and in the right ventricle during diastole, causing partial obstruction of the outflow tract (Fig. 4). The pulmonary artery could not be catheterized. Pressure in the right ventricular cavity was moderately elevated (50/2-6 mm Hg). A slight peripheral arterial oxygen desaturation (80 percent) was due to a right to left shunt at the atrial level noted in the cineangiocardiogram.

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Surgical findings and procedure: Surgery was undertaken in an attempt to relieve the obstruction to the blood flow through the right side of the heart. When the pericardium was opened, the external aspect of the heart appeared normal save for moderate enlargement of the right atrium and right ventricle. No tumor mass was felt on palpation of the heart. Circulation was arrested under deep hypothermia induced externally and with extracorporeal circulation. When the right atrium was opened, a long finger-like membranous sac was aspirated by the cardiac sucker. The base of this membranous sac was attached by four small pedicles, three at the atrial level and one in the right ventricle (Fig. 5A). In the atrium one pedicle was located at the upper part of the fossa ovalis just under the crista terminalis, another was in the inferior part of the atrium just above and to the right of the inferior vena cava; the third extended from immediately to the right of this latter pedicle to the tricuspid ring. The fourth point of attachment of this membrane was at the septal leaflet of the tricuspid valve extending down to its posterior chordae. This membranous sac measured about 5 cm from its insertion to its apex and extended from the right atrium at the level of the vena cavae to the outflow tract of the right ventricle.

Resection was easy and complete (Fig. 5B). However, on rewarming, the heart became distended because of a ductus arteriosus that had not been previously ligated; dissection was complicated by technical problems necessitating a second period of circulatory arrest. The infant did poorly afterward and died after surgery.

Postmortem examination showed no other pathologic features. The membrane was identified as a remnant of venous valve tissue obstructing outflow from the right ventricle because of its parachute-like movement from the right atrium into the outflow tract of the right ventricle in atrial systole.

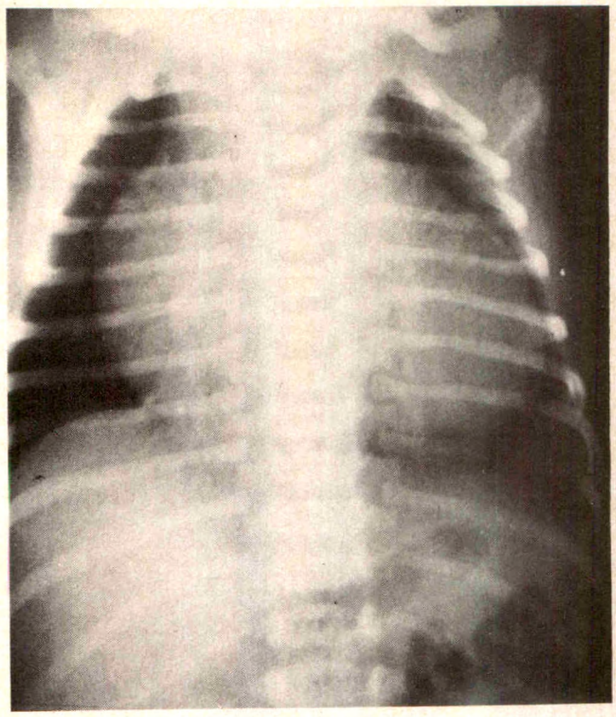


FIGURE 1. Chest roentgenogram at age 24 hours.

Comments

The valve of the sinus venosus at one stage of embryonic development nearly divides the right atrium into two chambers.[1] However, it normally disappears early in fetal life and, although anatomic vestiges of this valve are not rare, they are seldom responsible for obstructive lesions like the one in our case. Yater[1] described three cases in 1919, all associated with serious anomalies of the right ventricle and atresia or hypo-

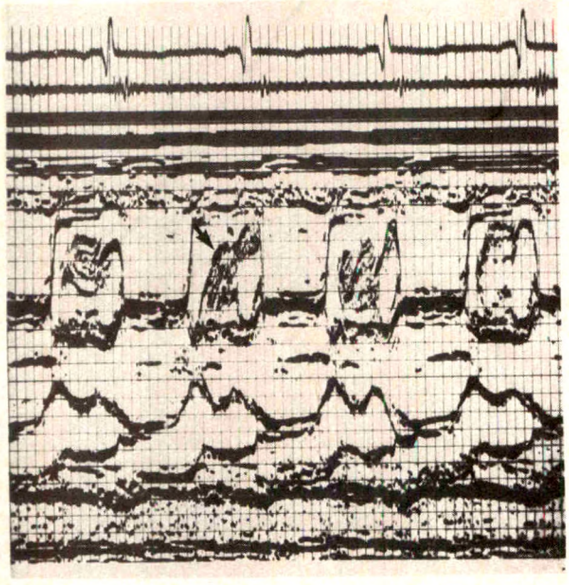


FIGURE 2. Echocardiogram of the right ventricular sinus showing a cloud of diastolic echoes (**arrow**) behind the anterior leaflet of the tricuspid valve.

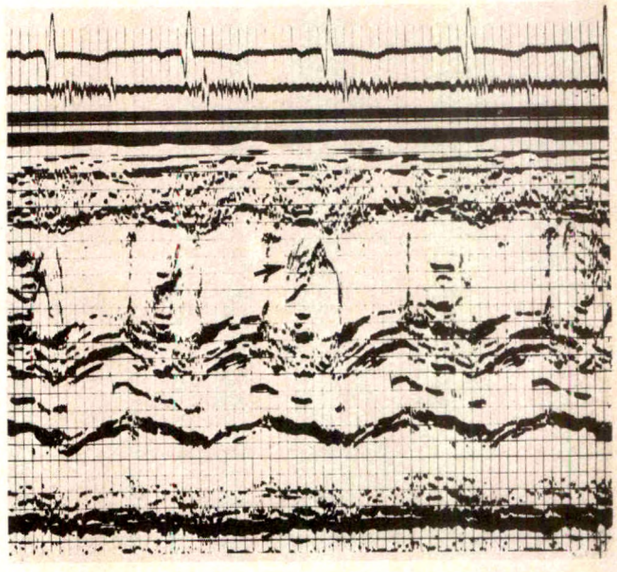


FIGURE 3. Echocardiogram taken at the level of the aorta showing abnormal echoes (**arrow**) appearing in the right ventricular outflow tract.

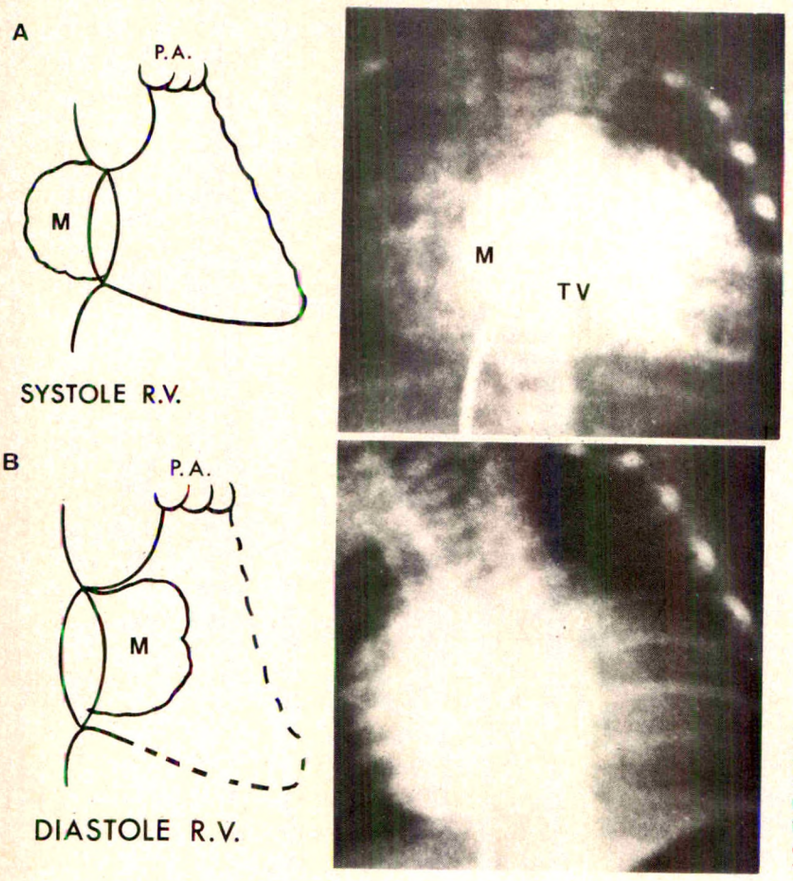


FIGURE 4. Angiocardiograms and corresponding diagrams. **A,** of the right ventricle, showing bulging of the membrane (M) in the right atrium during systole. **B,** of the right atrium, where the membrane is seen ballooning up to the right ventricular outflow tract during right ventricular diastole. P.A. = pulmonary artery; R.V. = right ventricle; T.V. = tricuspid valve.

plasia of the pulmonary or tricuspid valve, or both. Other reported cases[3,4] have usually been associated with the same type of anomaly.

To our knowledge, this is the first reported case with an echocardiographic study. The tracings obtained were suggestive of a myxoma of the right atrium. The few reported cases[5–9] of right atrial myxoma have in common the echocardiographic finding of a cloud of echoes penetrating the right ventricle during diastole, exactly as in our case. Some reported cases[6,7] also showed an increase in right ventricular dimension with paradoxical septal motion, probably secondary to tricuspid insufficiency and volume overload of the right ventricle. This finding was not present in our case. In addition, the extreme rarity of right atrial myxoma in infants[10] should help establish the diagnosis.

Because surgical correction of this serious anomaly may be possible, the diagnosis should be made soon after birth. The peculiar features in the echocardiogram suggesting a right atrial myxoma, a very unlikely diagnosis in infants, should be of value in the future evaluation and treatment of patients with this condition.

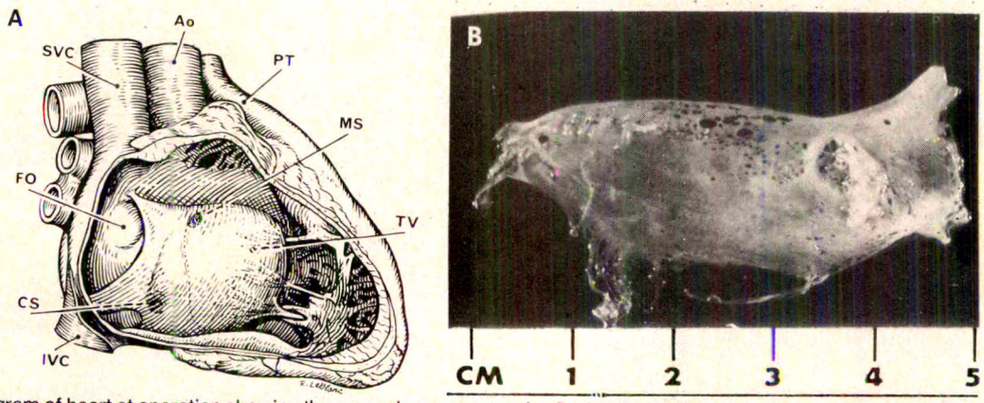


FIGURE 5. A, diagram of heart at operation showing the anomalous venous valve in situ. **B,** photograph of membrane removed at operation. Ao = aorta; CS = coronary sinus; FO = foramen ovale; IVC = inferior vena cava; MS = muscular septum; PT = pulmonary trunk; SVC = superior vena cava; TV = tricuspid valve.

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Echocardiographic Features of Supracristal Ventricular Septal Defect With Prolapsed Aortic Valve Leaflet

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Anatomically diagnostic echocardiographic features of a supracristal ventricular septal defect with prolapsed right coronary aortic leaflet are described in four children aged 2 to 10 years. Both single crystal M mode as well as 80° phased array sector scan techniques were used. The echographic features in the M mode scan from the aorta to the left ventricle in three of four patients included (1) the position of the ventricular septal defect as a clear space between the interrupted septal echoes below the aortic root, and (2) the prolapsed right coronary aortic leaflet as anomalous linear echoes in the right ventricular outflow tract. Angiographic, intraoperative and echocardiographic contrast studies were used to establish the diagnosis.

On sector scanning using the long axis view, the supracristal ventricular septal defect was recognized as a clear space between the top of the ventricular septum and the anterior segment of the aortic root in three of four patients. The right coronary aortic leaflet was seen to prolapse into the right ventricular outflow tract through this defect, and its motion could be clearly followed during systole and diastole. It is concluded that echocardiography provides anatomic diagnosis of this lesion. Furthermore, the severity and progression of this lesion can be assessed by quantitation of the left ventricular size and performance.

Aortic insufficiency resulting from prolapsed aortic valve leaflets through a ventricular septal defect occurs in 3 to 5.5 percent of all children with a ventricular septal defect.[1] The location of a ventricular septal defect may be infracristal (subaortic) or supracristal (subpulmonary).[2] A supracristal ventricular septal defect is almost always associated with prolapse of the right coronary aortic leaflet alone,[3] whereas in a subcristal variety either the right or the noncoronary leaflet is involved. This is an important lesion to diagnose early because its progressive nature results in increasingly severe aortic insufficiency and patients with this type of defect have a greater susceptibility to bacterial endocarditis than patients with a simple ventricular septal defect.[4] Anatomically diagnostic echocardiographic features of supracristal ventricular septal defect with prolapsed aortic valve have not previously been described.

The direct anatomic echocardiographic feature of a ventricular septal defect in a single crystal M mode scan is the presence of a clear space between interrupted interventricular septal echoes at the subaortic region. However, this sign is usually absent in the majority of patients with the most common type of ventricular septal defect, membranous. Recently, the presence of coarse vibrations in the pulmonary valve echogram was reported to be suggestive of a supracristal ventricular septal defect.[5] This sign is nonspecific, and we have found it difficult to separate these pulmonary valve vibrations from those observed in various other lesions with increased pulmonary blood flow.

This report concerns the diagnostic echocardiographic features of prolapsed aortic valve associated with a supracristal ventricular

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TABLE I

Hemodynamic and Echocardiographic Data on Four Patients With a Supracristal Ventricular Septal Defect

Case no.	Age (yr)	BSA	Echocardiographic Data					Catheterization Data					VSD Site
			LVED (cm)	EF (%)	VCf (circ/sec)	Ao (cm)	LA (cm)	Pressure (mm Hg) LVP	Ao	PA	RV_B	Qp/Qs	
1	9	1.12	4.8 126*	77	1.24	3.9 195*	2.3 100*	95/14	95/45 (70)	26/8 (16)	36/—	1.8	SC
2	2	0.56	3.9 115*	63	1.23	1.8 106*	2.0 91*	105/12	105/50 (80)	18/9 (14)	25/4	1.8	SC
3	10	0.80	4.2 111*	68	1.24	3.0 150*	2.1 91*	105/9	105/80 (90)	18/10 (14)	26/5	1.4	SC
4	4.5	0.35	4.8 141*	67	1.12	2.3 135*	2.4 109*	118/—	108/45	29/12	68/7	1.8	SC

* Percent of normal control values.
Figures in parentheses indicate mean values.
Ao = aorta; BSA = body surface area; circ = circumferences; EF = ejection fraction; LA = left atrium; LVED = left ventricular end-diastolic minor axis dimension; LVP = left ventricular pressure; PA = pulmonary artery; Qp/Qs = ratio of pulmonary blood flow to systemic blood flow; RV_b = right ventricular body; SC = supracristal; VCf = velocity of circumferential fiber shortening.

septal defect as observed with echocardiography in both the M mode single crystal and the real time phased array sector scanner techniques.

Material and Methods

Patients: Four patients, aged 2 to 10 years, with evidence of a supracristal ventricular septal defect were studied. The appearance of a murmur of aortic insufficiency suggested the presence of prolapsed aortic valve, and this diagnosis was confirmed at cardiac catheterization and, later, at operation in all four patients (Table I).

Echocardiography: Echocardiographic examination of the aortic root and the left ventricle was made in all four patients using a single crystal (2.25 and 3.5 megahertz) M mode Smith-Kline Ekoline echocardiograph coupled with an 1856 Honeywell strip chart recorder. Multiple scans from the aorta to the left ventricle were obtained from the second to the fourth intercostal space using standard sweep techniques. During cardiac catheterization in one child (Case 1), echocardiographic contrast studies were performed by injecting several 5 ml bolus doses of dextrose into the left ventricle. The position of the ventricular septal defect and prolapsed aortic leaflets was thus defined in the M mode echocardiogram.

Three patients (Cases 2 to 4) were additionally studied using real time, phased array 80° sector scanner (Varian Associates). A 2.25 megahertz transducer was used with an active area of 1.2 to 1.3 cm. Long axis, transverse, apical and subxiphoid views were studied.[6,7] The sector image was displayed on an x-y oscilloscopic screen at 30 frames/sec, and single frame photographs were subsequently obtained from a simultaneously recorded videotape.

Results

Hemodynamic and angiocardiographic findings: The echocardiographic and hemodynamic data of these four patients are presented in Table I. A small peak systolic pressure gradient (less than 10 mm Hg) was noted across the right ventricular outflow tract in three patients, and a moderate pressure gradient was present in the right ventricular body in the fourth. The ventricular septal defect on angiography was observed to be supracristal in all, and the right coronary aortic leaflet was also observed to be prolapsed into the right ventricular outflow tract, appearing as a small rounded mass at that site in three patients (Fig. 1). This prolapsed leaflet was responsible for the pressure differences observed across the outflow tract. In Case 4 the extent of the prolapse of the right coronary leaflet was slight, and the right ventricular mid cavity obstruction was due to a hypertrophied anomalous muscle bundle. The angiographic findings indicated that the aortic insufficiency was mild in Cases 2 and 3 and moderate in Cases 1 and 4 (Table I).

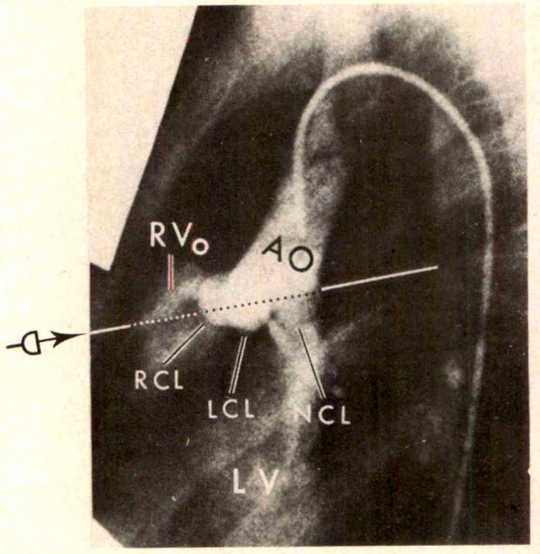


FIGURE 1. Case 2. Aortogram, lateral view. Prolapse of the right coronary aortic leaflet (RCL) is seen in late diastole as a rounded mass in the right ventricular outflow tract (RV_O). Opacification of the outflow tract occurs through the supracristal ventricular septal defect. There is aortic (AO) regurgitation into the left ventricle (LV) through the left (LCL) and noncoronary (NCL) leaflets. The **arrow** and **dotted line** represent the echocardiographic beam projection used to visualize the aortic root-left ventricular outflow tract in the M mode echocardiographic sweep.

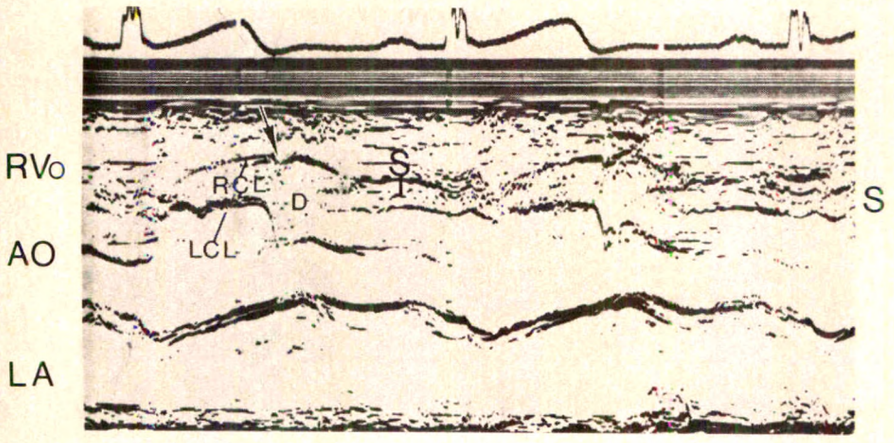


FIGURE 2. Case 1. Echocardiogram. The prolapsing right coronary aortic leaflet (RCL) is seen as a linear echo in the right ventricular outflow tract (RV_O) and shows a distinct diastolic closure (**arrow**) similar to that of the left coronary aortic leaflet (LCL) within the aortic root (AO). The supracristal ventricular septal defect (D) is represented by the clear space interrupting the septal echoes (S). Note an initial sharp anterior motion of the right coronary aortic leaflet during early systole with further anterior displacement during diastole. LA = left atrium.

M mode single crystal echocardiography: In three patients (Cases 1, 3 and 4) this procedure showed the ventricular septal defect as an open space between the interrupted interventricular septal echoes at the subaortic region (Fig. 2). In one patient (Case 2), the scan from the aorta to the left ventricle was inadequate for analysis because of technical reasons. The aortic root echo contained the usual anterior and posterior leaflet complexes showing normal separation during systole and closure during diastole. A third aortic leaflet was observed to have prolapsed into the right ventricular outflow tract and was seen as a linear echo. A scan from the aortic root to the left ventricle showed that the anomalous echoes due to the prolapsed right coronary leaflet in the right ventricular outflow tract were distinct from those produced by the anterior aortic root (Fig. 3).

The anomalous echo was seen to move anteriorly from the edge of the ventricular septal defect after the QRS complex of the electrocardiogram and returned sharply toward the ventricular septal defect at end-diastole. The motion of this echo was progressively anterior during early systole with a gentle plateau in mid systole and further anterior motion during diastole. A distinct diastolic closure motion was observed on this anomalous echo in the right ventricular outflow tract simultaneous with the diastolic closure motion of the other leaflets within the aortic root, confirming the identity of this leaflet as a part of the aortic valve apparatus (Fig. 2, 4 and 5). Angiographic studies in each patient identified the prolapsed leaflet as the right coronary leaflet.

Echocardiographic contrast study: In Case 1 this procedure confirmed the open space between the in-

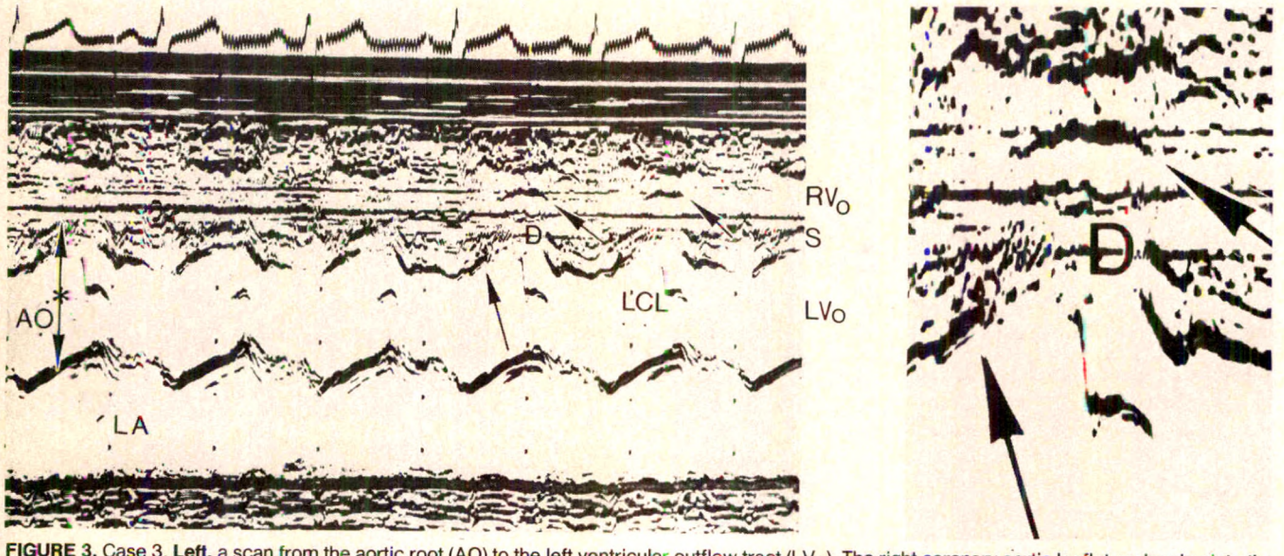


FIGURE 3. Case 3. **Left,** a scan from the aortic root (AO) to the left ventricular outflow tract (LV_O). The right coronary aortic leaflet prolapsing into the left ventricular outflow tract (RV_O) (**arrows**) is clearly a separate structure from the anterior segment of the aortic (AO) root (**asterisk**). Initial sharp motion of the right coronary aortic leaflet starting from within the aortic root (**first arrow**) through the ventricular septal defect (D) is seen (**second and third arrows**). **Right,** an enlarged view of this area. LA = left atrium; LCL = left coronary leaflet; S = septum.

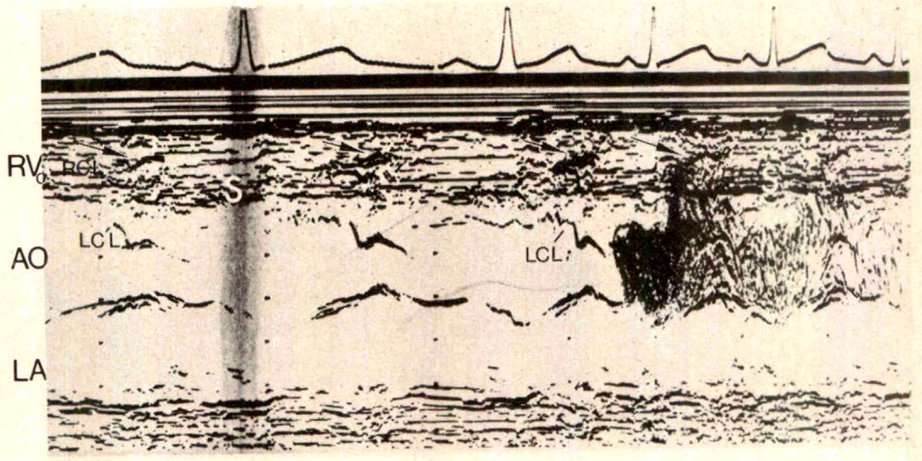


FIGURE 4. Case 1. Echocardiogram illustrating the right ventricular outflow tract (RV_O) at the approximate level of the transducer trajectory (see Fig. 1). Five percent dextrose injection into the aortic root (AO) resulted in opacification of the right ventricular outflow tract (**right side of figure**). Note the prolapsed right coronary aortic leaflet (RCL) distinguished by the diastolic closure motion (**arrows**); the left coronary leaflet (LCL) is seen within the aortic root. The echographic contrast material initially opacifies the aortic root and through the ventricular septal defect clearly delineates the right coronary aortic leaflet in the right ventricular outflow tract. S = septum.

terrupted septal echoes as a ventricular septal defect (Fig. 4). The contrast material injected into the aortic root was seen to opacify this space and to fill the right ventricular outflow tract. It initially coursed along the left ventricular surface of a linear echo in the right ventricular outflow tract delineating the position of the prolapsed right coronary cusp. Because the site of right coronary aortic leaflet prolapse is immediately distal to the anterior aortic root segment, careful scanning from the aortic root to the left ventricle is mandatory so that the anterior segment of the aortic root echoes is clearly separated from echoes due to a prolapsed right coronary aortic leaflet.

The distinctive echocardiographic features of a prolapsed right coronary aortic leaflet are: (1) location in the right ventricular outflow tract, anterior to the clear space (ventricular septal defect) between the interrupted septal echoes immediately below the aortic root; (2) sharp anterior motion through the ventricular septal defect in early systole; and (3) a diastolic closure notch similar in time to the aortic leaflets within the aortic root.

Phased array sector scanning: The long axis view of the left ventricle in the phased array sector scan in three patients (Cases 2 to 4) showed a defect between the top of the ventricular septum and the anterior segment of the root of aorta, which was slightly more craniad than the posterior segment (Fig. 6). This defect was located at the site normally occupied by the conal segment of the crista supraventricularis. The anterior aortic leaflet was seen to prolapse anteriorly and inferiorly from inside the aortic root through this defect into the right ventricular outflow tract. This leaflet was completely mobile during different phases of the cardiac cycle in two patients (Cases 1 and 3), and in the third patient (Case 4) the leaflet, although prolapsing anteriorly, was more inferiorly displaced and was somewhat restricted in its motion. The motion and position of the other aortic leaflets were normal.

Cardiac chamber and great vessel dimensions and ventricular function measurements: These data were derived from M mode echocardiograms and the values compared with published control values.[8] The aortic root was enlarged in three patients (Cases 1, 3,

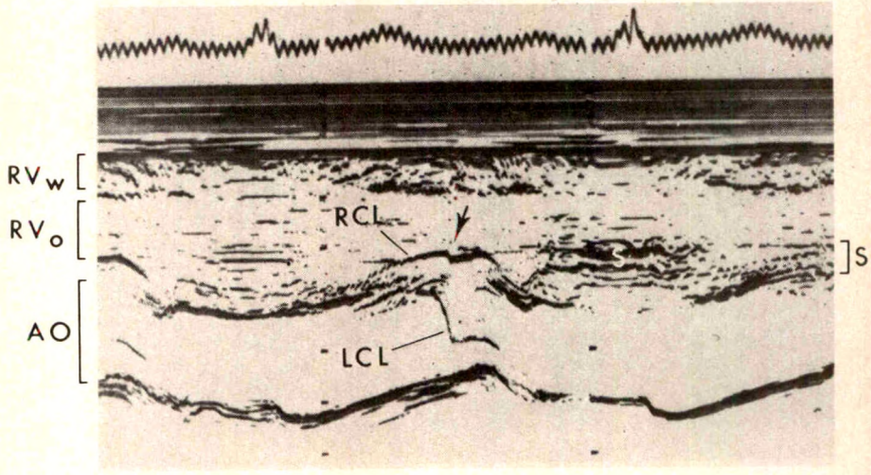


FIGURE 5. Echocardiogram from an additional patient with supracristal ventricular septal defect (not included in the study group) shows the position of the prolapsed right coronary leaflet (RCL) in the right ventricular outflow tract (RV_O). A distinctive diastolic closure motion (arrow) on this leaflet occurs simultaneously with that on the left coronary leaflet (LCL) within the aortic root (AO), which confirms the identity of this echo as part of the aortic valve apparatus. RV_W = right ventricular wall; S = septum.

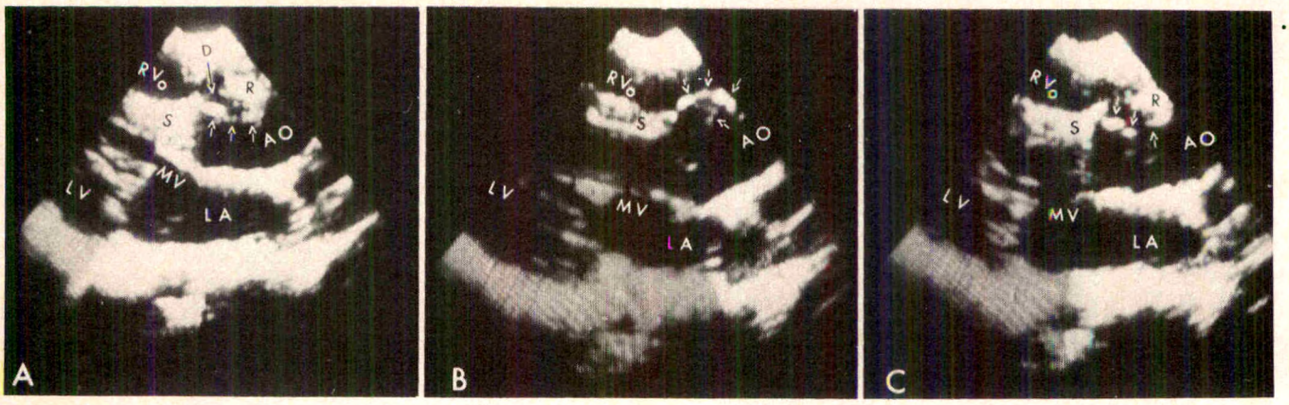
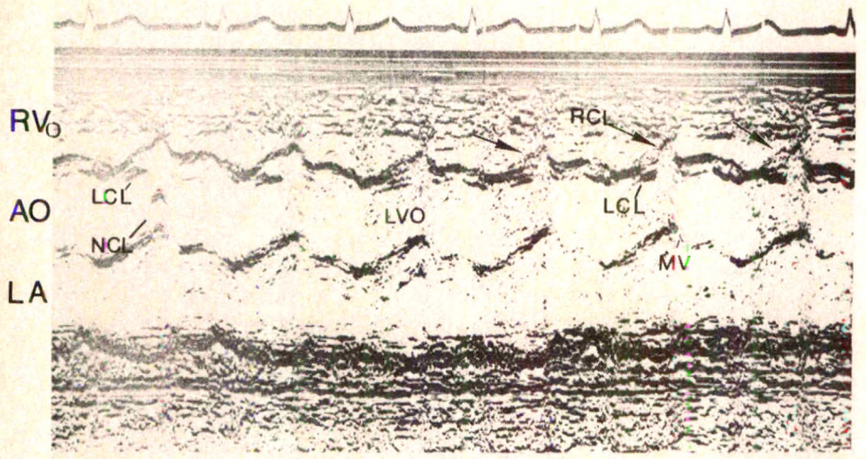


FIGURE 6. Case 3. Long axis views of 80° sector scan of aorta (AO) and left ventricular (LV) outflow tract during different phases of the cardiac cycle. **A,** the ventricular septal defect (D) is located between the anterior segment of the aortic root (R) and the septum (S). The right coronary leaflet (**white arrows**) is seen prolapsing across the defect into the right ventricular outflow tract (RV_O) in late diastole. The mitral valve (MV) is completely open. **B,** marked degree of prolapse in mid diastole. **C,** mild degree of prolapse in early systole. The other two leaflets are faintly seen within the aortic root. LA = left atrium.



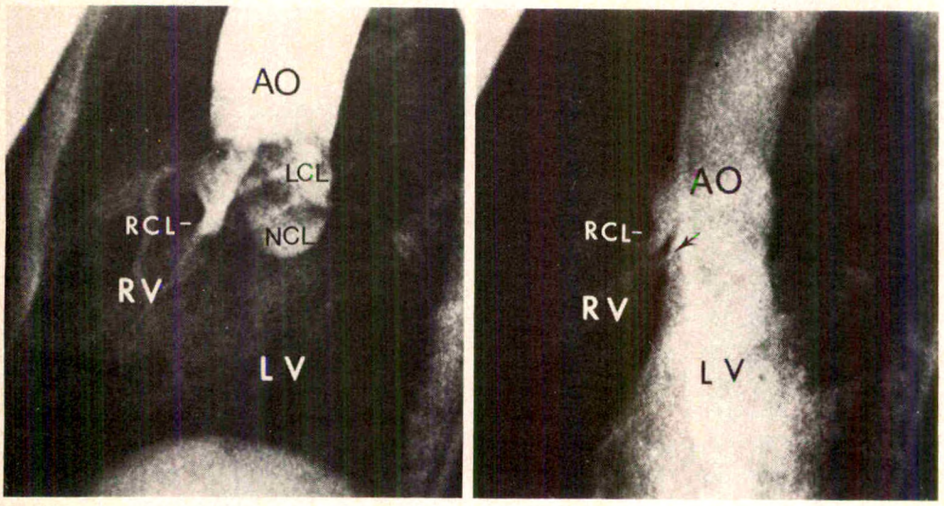


FIGURE 7. Additional case not included in this study. **Top,** M mode scan of aorta (AO) to the left ventricular outflow tract (LVO) shows the prolapsed right coronary leaflet (RCL) (**arrow**) immediately below the aortic root. Left coronary (LCL) and noncoronary (NCL) leaflets are located within the aortic root as in normal subjects. MV = mitral valve; S = septum. **Bottom,** lateral view cineangiogram of aorta (**left**) and left ventricle (LV) (**right**) during systole. An early stage of the prolapse of the right coronary leaflet into the right ventricular outflow tract (RV) is shown. The contrast material is shunting into the right ventricular outflow tract through a ventricular septal defect (**arrow**) that is partially occluded by the right coronary leaflet.

and 4). The left ventricular size was increased in two patients (Cases 1 and 4) whose angiograms indicated moderate aortic insufficiency. The left ventricular ejection fraction and circumferential fiber shortening velocity were within normal limits of all four patients.

Discussion

Our study shows that single crystal M mode echocardiography can help identify the anatomic location of the supracristal ventricular septal defect as a space between the interrupted septal echoes in the subaortic region. The echocardiogram revealed two leaflets within the aortic root, an anterior and a posterior one, showing normal opening and closure movements during the cardiac cycle. The third leaflet, identified angiographically and intraoperatively as a right coronary leaflet, was seen to have prolapsed into the right ventricular outflow tract and appeared as a linear echo. These observations suggest that normally the aortic root echocardiogram displays the left and noncoronary leaflets and not the right and noncoronary leaflets as has been suggested.[9,10]

The supracristal type of ventricular septal defect results from deficiency of conal tissue. Thus the ventricular septal defect permits communication between the anterior part of the aortic root and the right ventricular outflow tract below the pulmonary valve. Because normally this tissue provides mechanical support to the right coronary aortic leaflet, this leaflet prolapses and hangs inferiorly and anteriorly into the right ventricular outflow tract and may cause systolic pressure differences between the right ventricle and pulmonary artery.

Patterns of motion of the prolapsed aortic leaflet: The patterns of motion observed in our echocardiographic study are consistent with those described by Tatsuno et al.[11] from angiographic data. The left to right shunt through the ventricular septal defect initiates the prolapse during early systole. During mid systole, the leaflet motion stabilizes and there is anterior displacement of the anterior aortic root. During diastole, further progression of the prolapse occurs as a result of the diastolic aortic pressure. This latter motion produces separation of the prolapsed cusps from the other leaflets and results in aortic insufficiency. The anterior motion of the observed anomalous echo representing the prolapsed right coronary cusp in our patients followed these expected patterns of motion during the cardiac cycle.

Diagnostic value of echocardiography: Sector scanning provides a unique view of the movements of the prolapsed cusp so that the degree of mobility can be assessed. Because a fixed leaflet would be expected to produce greater aortic insufficiency,[11] selection of patients for early corrective surgery can thus be made from the echocardiographic examination. Furthermore, echocardiography provides not only an anatomic diagnosis of this lesion, but also a quantitative assessment of left ventricular size and function.

Our study group did not include patients with a subcristal ventricular septal defect and a prolapsed aortic leaflet. However, some anatomic features of this type of defect—that is, partial deficiency of the crista supraventricularis and congenital weakness of the sinus of Valsalva—are similar to the supracristal variety. Echocardiographically, the prolapsed aortic leaflet would be expected to be lower in the right ventricular outflow tract and the ventricular septal defect somewhat more caudal in location than the supracristal type. Thus, combined single crystal and sector scan echocardiography may also prove to be of diagnostic value in patients with a subcristal ventricular septal defect.

Clinical implications: Echocardiography reveals anatomically diagnostic features of a supracristal ventricular septal defect with a prolapsed aortic valve and permits noninvasive longitudinal assessment of factors such as left ventricular function, degree of valve prolapse and mobility and severity of aortic insufficiency. Since submission of this manuscript we used M mode echocardiography to diagnose two additional cases of supracristal ventricular septal defect and prolapsed right coronary aortic leaflet in its early stage (Fig. 6 and 7, top). Aortic regurgitation was not present in either case. Angiography confirmed the diagnosis in both patients (Fig. 7, bottom).

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Propranolol in Human Plasma and Breast Milk

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To assess the problem of continuing propranolol therapy in a breast-feeding mother, studies were performed to determine simultaneously plasma and breast milk concentrations of propranolol after single dose (40 mg) and continuous dose (40 mg 4 times daily) treatment with this drug. Breast milk and plasma concentrations of propranolol peaked between 2 and 3 hours after dosing. Propranolol concentrations in breast milk were less than 40 and 64 percent, respectively, of peak plasma propranolol concentrations after single dose and continuous dose administration. It was estimated that the maximal cumulative propranolol load to this breast-feeding infant, consuming 500 ml of whole milk, when the mother received 40 mg of propranolol 4 times daily would be 21 μg/24 hours. This dose is considerably less than the usual therapeutic dose of propranolol for infants.

There are limited published data to assist the physician deciding whether to continue propranolol therapy in a breast-feeding mother. The current widespread use of propranolol and its recognized toxic manifestations of respiratory depression, hypoglycemia and bradycardia in neonates make this an important clinical question.[1–3]

To provide further information on propranolol concentrations in breast milk and their relation to plasma concentrations we measured these concentrations simultaneously in a hypertensive postpartum woman after single dose (40 mg) and continuous dose (40 mg 4 times daily) propranolol therapy.

Methods

Patient and protocol: A 30 year old white postpartum woman, suffering from palpitations (unifocal ventricular premature beats) and hypertension, agreed to participate in the study. She had been treated for these conditions with a diuretic drug (Dyazide®) and propranolol for 2 years. During her pregnancy, diuretic therapy was discontinued; 24 hours before delivery propranolol (40 mg 4 times daily) was discontinued. The study was approved by the University of Missouri Committee for Research Involving Human Subjects and the patient gave informed consent.

The patient gave birth to a normal 2.7 kg male infant on January 10, 1978 and began breast-feeding. Diuretic therapy was resumed on February 3, but her blood pressure and palpitations were inadequately controlled. On February 23 and 28, she underwent studies to determine plasma and breast milk concentrations of propranolol before and at 1 hour intervals after ingesting 40 mg of propranolol in a single dose. On each occasion, breast-feeding was discontinued for 12 hours after the administration of propranolol. On March 4, she began taking propranolol, 40 mg 4 times daily, continuously without curtailment of breast-feeding. On March 6, a study was performed to determine plasma and breast milk concentrations of propranolol in the mother. After these studies, the propranolol dosage was increased to 240 mg/day. After 30 days, a pre-dose and a 3 hour post-dose breast milk sample was obtained for quantitation of propranolol concentration.

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Sample collection and analysis: Whole blood samples (10 ml) were obtained from a forearm vein using a heparinized glass syringe. Plasma was separated from the red cells by centrifugation and was frozen until analysis. The breasts were emptied of milk (approximately 5 ml after the initial sample) at each sampling period. Breast milk samples were pooled to provide a representative sampling from both breasts and were frozen until analysis.

Plasma and breast milk concentrations of propranolol were determined by a modification of the method of Shand et al.[4] Samples were made alkaline, and the propranolol was extracted into a mixture of 2 percent isoamyl alcohol in *n*-heptane. The propranolol was then partitioned from the organic phase into 0.1 N hydrochloric acid. This acidic phase was analyzed spectrofluorometrically, and propranolol concentration was determined from a standard curve prepared by the extraction of aqueous standards of propranolol hydrochloride.

Results

Single dose propranolol: Plasma and breast milk concentrations of propranolol after the administration of a single 40 mg test dose of propranolol are shown in Table I. Both plasma and breast milk concentrations of propranolol peaked between 2 and 3 hours after administration of propranolol. Breast milk concentrations were less than 40 percent of peak plasma propranolol concentrations.

Continuous dose propranolol: Plasma and breast milk propranolol concentrations after the continuous administration of propranolol, 40 mg 4 times daily, are shown in Figure 1. Plasma and breast milk concentrations peaked 3 hours after dosing, and the peak breast milk concentration was 64 percent of the corresponding plasma concentration. There were equal concentrations of propranolol in plasma and breast milk 8 hours after the last dose of 40 mg (0 hours). After a 30 day regimen of 240 mg/day propranolol, the pre-dose and 3 hour post-dose propranolol concentrations in breast milk were 26 and 64 ng/ml, respectively. No symptoms or signs of respiratory depression, hypoglycemia or bradycardia were observed in the infant throughout the periods of propranolol administration to the mother.

Discussion

The administration of any drug to a lactating woman is potentially hazardous to the breast-feeding infant, especially if toxic concentrations are ingested. The benefits of breast-feeding to both mother and infant are well recognized.[5,6] There has been a lack of accurate knowledge concerning whole milk concentrations of propranolol in lactating women receiving propranolol therapy. Indeed, misinformation has been published. It was reported[7] in 1973 that a maximal dose of 15 to 20 mg of propranolol/day could be ingested by a nursing infant from a mother receiving a 40 mg oral dose. However, the propranolol concentration units reported were in error (they should have been 15 to 20 μg/24 hours), and the retraction was not published until 1976.[8]

To our knowledge, the only published data on propranolol therapy in breast-feeding mothers are in a letter to the editor by Karlberg et al.[9] In their study, two nursing mothers received propranolol in single oral doses ranging from 20 to 160 mg, at intervals of several days. The concentration of total propranolol in the plasma and in breast milk was estimated over a period of 3 hours. Propranolol was found to penetrate into the breast milk in a dose-dependent manner. The milk to plasma ratio was reported to be approximately 1.

TABLE I
Propranolol Concentration (ng/ml) in Breast Milk and Plasma After Single Dose Therapy

	2/23/78		2/28/78	
Time*	Breast Milk	Plasma	Breast Milk	Plasma
0	0	0	0	0
1	0	7	0	0
2	4	18	8	17
3	4	17	9	23
4	4	16	9	19
5	2	13	4	12

* Hours after administration of a single dose of propranolol (40 mg).

In our study, propranolol concentrations in plasma and breast milk obtained after single dose and continuous dose drug regimens suggest a plasma to breast milk concentration ratio of 2.5:1 and 1.5:1, respectively. The elimination of propranolol after peak drug concentrations does not suggest preferential storage or elimination of propranolol by way of the breast. Increased concentrations of propranolol in breast milk after the 30 day dosage regimen (240 mg/day) were expected. In addition to a dose-dependent relation between propranolol ingestion (mg/kg) and plasma concentration, the long-term administration of propranolol has been

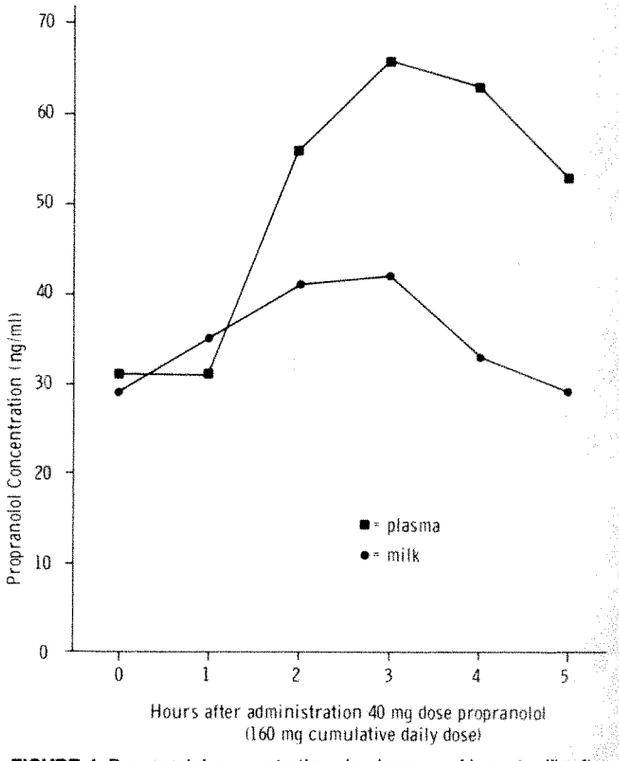


FIGURE 1. Propranolol concentrations in plasma and breast milk after continuous dose administration (40 mg 4 times daily).

shown to result in increased plasma concentrations and a longer elimination half-life.[10]

Therapeutic implications: Using the peak propranolol concentration after dosage at 160 mg/day (42 ng/ml of propranolol in breast milk) and assuming that the infant's total ingestion will not exceed 500 ml/day (usual infant milk ingestion 100 to 150 ml/kg per day), the maximal cumulative propranolol load would be 21 μg/24 hours. Using the peak propranolol concentration after dosage at 240 mg/day for 30 days (64 ng/ml propranolol in breast milk), the maximal cumulative propranolol load would be 32 μg/24 hours. Assuming 100 percent bioavailability and a 4 kg infant, this latter dose would represent a dietary intake equivalent to 8 μg/kg body weight.

Currently, therapeutic dosage of propranolol for infants and small children has not been established. Recommended dosages have ranged from 0.2 to 0.5 mg/kg per day[11] to 0.5 to 2.0 mg/kg per day.[12] The dosage ingested by the breast-feeding infant would therefore be approximately 1/100 of that used for therapeutic purposes. However, hepatic microsomal enzyme systems responsible for metabolism are immature in newborn infants, and an accumulation of this drug might be expected to be beyond that anticipated in older patients.[13] Therefore, close observations for bradycardia or evidence of hypoglycemia should be carried out in these nursing infants.

Acknowledgment

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Retrograde Properties of the Fast Pathway in Patients With Paroxysmal Atrioventricular Nodal Reentrant Tachycardia

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In this issue of the Journal, Gomes and co-workers[1] present evidence suggesting that some patients with apparent atrioventricular (A-V) nodal reentrant paroxysmal tachycardia in fact possess an accessory pathway utilized for retrograde conduction. They hypothesize that this pathway bypasses all or part of the A-V node. They support their conclusion by noting that retrograde conduction in some patients with apparent A-V nodal reentry is not A-V nodal-like in quality, in regard to pacing and ouabain responses. In this editorial, we present our thoughts concerning retrograde conduction in patients with A-V nodal reentrant paroxysomal tachycardia.

Dual A-V Nodal Pathways

A-V nodal reentrance appears to be the most common mechanism of paroxysmal supraventricular tachycardia in human beings.[2–10] In the majority of patients with A-V nodal reentry, studies utilizing atrial stimulation suggest the presence of two functional anterograde A-V nodal pathways, one fast and one slow (this diagnosis depends on demonstration of discontinuous conduction curves with the atrial extrastimulus technique).

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It has been hypothesized that A-V nodal reentrant paroxysmal tachycardia in these patients usually reflects the presence of such dual A-V nodal pathways. Induction of paroxysmal tachycardia usually reflects anterograde failure of the fast A-V nodal pathway with resultant anterograde slow pathway conduction. The pathway that failed to conduct anterograde then appears to be utilized for retrograde conduction, so that circus movement reentrant tachycardia results. The components of the circus movement appear to be the slow A-V nodal pathway as the anterograde limb and the fast A-V nodal pathway as the retrograde limb. Both proximal and distal common pathways appear to be intranodal.[11] In a less common type of A-V nodal reentrant paroxysmal tachycardia, the fast pathway is the anterograde limb and the slow pathway the retrograde limb.[12]

It is reasonably well substantiated that the fast anterograde pathway in these patients is A-V nodal, in that the A-H interval of the fast pathway increases with shortening of the atrial paced cycle length, and that refractoriness of the fast pathway is increased by shortening of cycle length and also by administration of digitalis and propranolol.[3–5] Conversely, the conduction time and refractory periods of the anterograde fast pathway are decreased by atropine.[13] The anterograde slow pathway possesses electrophysiologic properties that are almost identical to those of the anterograde fast pathway, so that it also is an A-V nodal pathway.[3–5,13]

Gomes et al.[1] imply that a substantial number of patients with A-V nodal reentrant paroxysmal tachycardia have in fact a third and different pathway that

* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal or of the American College of Cardiology.

conducts in retrograde fashion. One could then ask, (1) Is this third pathway specifically associated with the presence of dual anterograde pathways, or (2) does it occur in many patients with and without dual A-V nodal pathways?

If the answer to the first question is yes, then there should be a substantial number of patients with dual A-V nodal pathways who are capable of having at least two paroxysmal tachycardias, one tachycardia characterized by anterograde fast pathway conduction (and the third pathway for retrograde conduction) and one tachycardia characterized by anterograde slow pathway conduction (and the third pathway for retrograde conduction). This type of phenomenon has been noted in patients with dual anterograde A-V nodal pathways and Wolff-Parkinson-White syndrome, who have manifest ability for two A-V reentrant tachycardias (anterograde fast and retrograde Kent pathways as well as anterograde slow and retrograde Kent pathways).[14] If the answer to the second question is yes, then there should be a substantial number of patients with paroxysmal supraventricular tachycardia with circus movement consisting of the normal A-V node as the anterograde limb and the tract described by Gomes et al. as the retrograde limb. In our experience, there is not such a large group. Reports[9,10] available thus far suggest that approximately 10 to 20 percent of paroxysmal supraventricular tachycardias reflect the presence of concealed Kent bundles with retrograde conduction (A-V muscle bundles with retrograde conduction). However, these concealed pathways have specific conduction properties that are different from those proposed by Gomes et al.

Properties of the Retrograde Pathway

If one examines the properties of the retrograde pathway in patients with apparent A-V nodal reentry due to dual A-V nodal pathways, one delineates a number of surprising and some not so surprising properties. The following observations can be made concerning the retrograde properties of the fast pathway in patients with dual A-V nodal pathways and A-V nodal reentry: (1) There is frequently either no or only a minimal increment in ventriculoatrial conduction time or His bundle-atrial conduction time when one studies these patients with incremental ventricular pacing.[13,15-17] In most of the patients, a ventricular paced rate can be achieved at which ventriculoatrial block is demonstrated (usually type I, although type II or 2:1 block is sometimes noted). (2) A similar lack of increase in the V-A or the H-A interval is often noted with ventricular extrastimulus testing.[13,15-17] (3) Ventricular extrastimulus testing demonstrates that at close coupling intervals, in many of these patients, as the V-H interval increases, the H-A interval increases simultaneously, suggesting that the His bundle and the low septal right atrium are in series (ruling out an extranodal anomalous pathway). (4) The H-A interval during paroxysmal supraventricular tachycardia or during ventricular pacing is relatively short. (5) Ouabain has little or no depressant action on the retrograde fast pathway.[18] (6) Procainamide selectively depresses retrograde fast pathway conduction.[19] (7) Atropine facilitates retrograde fast pathway conduction.[13]

Thus, the fast pathway with retrograde conduction is Purkinje-like in many of its properties. However, it is quite clear, because of atropine responsiveness, that at least part of this pathway is A-V nodal. One explanation for the unusual properties of this pathway is that it may be anatomically a different pathway from the fast pathway, conducting anterograde and that there may be three pathways. Although this may turn out to be the case, we prefer another explanation for reasons elucidated in the preceding discussion of the hypothesis of Gomes et al.[1] We thus postulate that there is a major asymmetry in A-V nodal conduction and that anterograde fast pathway conduction and retrograde fast pathway conduction are different because of the geometry of these pathways. There is certainly precedent in electrophysiology for asymmetry of anterograde and retrograde conduction in a single pathway. A good example of this is the demonstration of concealed Kent bundles that are capable of conducting only in a retrograde direction. The cause of the functional asymmetry of the fast A-V nodal pathway might well reside in the difference of input in anterograde as opposed to retrograde conduction.[20-22] In anterograde conduction, the input to the A-V node is by way of atrial approaches, which may consist of atrial cells with somewhat A-V nodal-like properties.[23] The retrograde input into the A-V node is quite different, occurring primarily from the rapidly conducting His bundle. It is quite possible that the difference in velocity of input (anterograde versus retrograde) might affect the conducting properties of the A-V node and its pharmacologic responses.

It is the behavior of the anterograde slow and retrograde fast pathway that determines whether a given patient is capable of having A-V nodal reentrant paroxysmal tachycardia. The difference between the patients with a dual pathway who can and cannot have paroxysmal supraventricular tachycardia resides in quantifiable anterograde slow pathway and retrograde fast pathway properties.[16] These conduction properties are easily determined utilizing rapid atrial incremental and rapid ventricular incremental pacing. If a patient with dual A-V nodal pathways cannot sustain paroxysmal tachycardia, this inability reflects inadequate conduction in either the anterograde or retrograde limb of the circus movement.[13,16] Inadequate conduction in either the anterograde slow or retrograde fast pathway can sometimes be reversed with atropine, which may thus facilitate demonstration of A-V nodal reentrant paroxysmal tachycardia.

Therapeutic Implications

When attempting to define effective prophylactic therapy for prevention of recurrent paroxysmal A-V nodal reentrant tachycardia, a knowledge of the pharmacology and properties of anterograde slow and retrograde fast pathways is of value. In some patients, tachycardias may be prevented by depression of the

anterograde slow pathway, so that this pathway cannot serve as the anterograde limb for repetitive reentry. Drugs that may depress the anterograde slow pathway include digitalis, propranolol and verapamil.[3,4,18,24] Loss of the ability to sustain paroxysmal tachcardia due to these drugs will be accompanied by demonstration of an increase in the atrial paced cycle length producing A-V nodal (slow pathway) Wenckebach periodicity to a cycle length greater than the cycle length of spontaneously occurring tachycardia.[13,16] In some patients, tachycardias may be prevented by depression of retrograde fast pathway conduction. Drugs that may depress the retrograde fast pathway include procainamide and, probably, quinidine.[19] Loss of the ability to sustain paroxysmal tachycardia due to these drugs will be accompanied by an increase in the ventricular paced cycle length producing ventriculoatrial block to a cycle length greater than that of spontaneously occurring tachycardias.[13,16] These drug effects may be demonstrated during a short term electrophysiologic study (on a single occasion in the catheterization laboratory) or over several days (long-term electrophysiologic study), utilizing a temporary electrode catheter and serial drug administration.[25,26]

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LETTERS TO THE EDITOR

BYPASSING THE BYPASS WITH PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Coronary bypass surgery, now a decade old, still generates widespread controversy. Divergent points of view among competent cardiologists exist regarding its indications, risks, long-term accomplishments and cost. It may be many years before these issues are resolved. For these reasons, it is important to pursue and test medical and surgical alternatives that may replace or complement bypass surgery in the treatment of coronary artery disease.

Percutaneous transluminal coronary angioplasty is a promising new nonsurgical method for the relief of coronary arterial stenosis in selected cases. It was developed by Andreas Gruentzig at the University of Zurich, who first applied it successfully on September 16, 1977 in a patient with proximal obstructive noncalcific coronary disease. The blockage was completely eliminated.[1]

Technique of procedure: The procedure is performed in the cardiac catheterization laboratory and generally takes less than 2 hours to complete. A preformed guiding catheter, similar to the ones used for coronary angiography but not tapered at its tip, is advanced from the femoral artery in the groin over a guidewire into the aortic root and engaged in the orifice of the affected coronary artery without occluding it. A double lumen dilating (balloon) catheter, 1.2 mm in external diameter with the balloon deflated, is threaded through the guiding catheter into the stenosed coronary artery until it lies astride the site of obstruction. One lumen of the dilating catheter, reaching its tip, monitors the blood pressure during catheter advancement. The second lumen leads through side holes into a sausage-shaped segment (balloon) near the tip which can be filled by an appropriate pump with diluted contrast medium to an adjustable balloon pressure of 3.5 to 5 atmospheres. At 5 atmospheres a maximal external balloon diameter of 3.0 or 3.7 mm is attained, depending on the catheter model. The balloon is made up of highly resistant polyvinyl chloride whose pressure-dependent stretch is minimal over the operative pressure range of 3.5 to 5 atmospheres.

The filling phase of the balloon lasts for 5 to 15 seconds and is followed by pump-activated deflation; chest pain usually does not develop during the maneuver. When inflated, the balloon exerts a force perpendicular to the long axis of the vessel; this force compresses the low density content of a recent atheroma against the outer layers of the vessel wall and redistributes it within the wall to yield often a normal vessel diameter as judged from angiographic criteria. If the result is only partially successful, the sequence of inflation and deflation can be repeated.[2]

Indications: The interest generated by percutaneous transluminal coronary angioplasty, as expected, has been intense. For this reason, an informal meeting was called in January 1978 in Zurich to train a small number of cardiologists in the procedure and to establish guidelines during its initial developmental period. A strict protocol was devised.

Patients are accepted for the procedure at the designated centers in Zurich, Frankfurt, San Francisco, New York and Philadelphia and Boston who meet the following criteria: (1) under age 60, (2) a history of angina of less than 1 year; (3) critical (more than 70 percent reduction of coronary lumen) proximal stenosis of a major coronary vessel that is not calcified, (4) good quality of this vessel past the obstruction, (5) good ventricular function, and (6) positive exercise thallium scan.

Current results: In August 1978, the first Zurich conference, open to a larger audience, was convened, procedures, demonstrations and the results discussed and summarized. As of August 15, 1978 percutaneous transluminal angioplasty has been attempted in 66 patients, in 30 by Dr. Gruentzig alone. Successful dilatation was achieved in 39 patients, generally with little (less than 30 percent reduction of luminal diameter) or no residual stenosis. All patients left the hospital within 48 hours and most returned to their job within 1 week. This group included three patients in whom discrete, critical lesions that had developed in coronary bypass grafts were relieved. The angiographic follow-up in some of these patients, although not exceeding 5 months, failed to reveal recurrence of the obstruction. In 27 patients the attempted procedure was unsuccessful because of the inability either to reach the lesion or, less often, to advance the dilating catheter through a particularly tight and presumably hard stenosis. In 6 of these 27 patients chest pain or acute S-T segment changes in the electrocardiogram, or both, developed with angiographic evidence of further reduction or interruption of blood flow through the diseased artery. In some of these patients the evidence pointed to penetration of the obstructing atheroma by the catheter tip. All six patients underwent successful emergency coronary bypass surgery within 3 hours without the development of myocardial infarction as assessed from electrocardiographic or serum or enzyme criteria.

Future prospects and implications: What is the future of coronary dilatation, and what are its shortcomings? The procedure is feasible, but almost everything else about percutaneous transluminal coronary angioplasty remains to be established. Despite some preliminary observations by Gruentzig and others, the type and extent of damage caused by the balloon to the coronary endothelium and the consequent interaction between injured endothelium and formed and humoral blood factors need to be investigated in depth. The immediate effect of compression on the density, architecture and redistribution of the atheromatous contents within the wall will have to be studied together with the long-term effects on the plaque: reaccumulation?, reabsorption?, fibrosis?. Progress in related fields could be expected from this research. At the clinical level, the subjective and objective (hemodynamic, geometric and myocardial metabolic) effects of successful coronary dilatation will need quantification at rest and during stress using both invasive and noninvasive means. The risks of the procedure will have to be enumerated and the complications quantitatively identified. The range of indications and contradictions will have to be established and carefully defined. Eventually, the long-term results of percutaneous transluminal coronary angioplasty will need to be determined.

If basic research and clinical investigation provide favorable answers, then promising new applications can be envisioned for percutaneous transluminal coronary angioplasty, including

its combination with bypass surgery at the operating table. However, given the limitations of the technique, which stem mainly from catheter size and plaque consistency, it is doubtful that this procedure will every replace coronary bypass surgery in more than 15 percent of the operative candidates. Yet, given the prevalence of obstructive coronary artery disease and the scope of coronary surgery today, the impact on hospital and patient costs could be substantial.

Despite the uncertainty regarding its ultimate role in the management of proximal obstructive coronary disease, percutaneous transluminal coronary angioplasty is an exciting technique that offers still another means of relieving angina and improving myocardial perfusion. As experience is increased in the designated medical centers, the feasibility of this concept will be fully tested. However, hasty judgments about its effectiveness must be discouraged and the errors of the past, particularly in the accumulation of reliable statistical data, must be avoided.

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NHLBI POSITION ON PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA)

In 1959, Mason Sones reported on selective coronary arteriography, a technique that quickly became the "gold standard" for precise diagnosis of coronary artery disease. In the early 1960's Dotter and Judkins introduced the original concept of utilizing a catheter to dilate an atherosclerotic obstruction in a peripheral artery. Now, almost two decades later, the selective coronary catheter is being proposed as a direct therapeutic tool for correction of coronary obstructive lesions where heretofore it has only been diagnostic.

In 1977, Andreas Gruentzig and his colleagues in Zurich, Switzerland, reported a technique that is now limited to research evaluation but that might in the future offer promise as a standard therapeutic approach for selected patients. This technique utilizes a double lumen dilatation catheter with a balloon with unique expansive characteristics and an appropriate pump to deliver and quickly remove a specified pressure. Utilizing special guiding catheters, the dilatation catheter can be manipulated through the site of obstruction in a coronary vessel under direct fluoroscopic observation. The balloon can then be inflated with subsequent compression of the lesion and dilatation of the functional lumen of the coronary artery. By mid August 1977 Gruentzig and his colleagues had used this procedure in 30 patients. In 19 cases the procedure has been successful in dilating the affected coronary artery and relieving the patient's symptoms. There have been two acute myocardial infarctions and one case of unstable angina reported in conjunction with the procedure but no deaths. Patients with obstructions that could not be dilated by percutaneous transluminal coronary angioplasty were offered immediate bypass surgery.

On the basis of this early reported experience, it appears that percutaneous transluminal coronary angioplasty has limited promise as a therapeutic technique for a small number of categories of patients with obstructive coronary disease. It also appears that this technique is technically demanding and there is definite risk of myocardial infarction and possible death even in the hands of skilled operators experienced in this special technique who exercise care in applying it only to appropriate patients. The caution against the use of this research technique without such special experience and meticulous case selection should be evident.

In order to evaluate most completely and expeditiously the promise and limitations of this new technique, the National Heart, Lung, and Blood Institute proposes to establish an initial inventory of those investigators who are initiating clinical studies of this research technique in the United States. To this end, we have established a preliminary Interim Registry on Percutaneous Transluminal Coronary Angioplasty to be maintained by the Cardiac Diseases Branch, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute. Investigators interested in participating in this Interim Registry are invited to submit a copy of their protocols, including their indications for the procedure, a brief summary of baseline data on the patients studied, as well as information on outcome.

A workshop on percutaneous transluminal coronary angioplasty is planned to be held in Bethesda in June 1979 for discussion of the technique. This workshop will provide a forum for reviewing the preliminary data collected on this technique in this country by the Interim Registry. Workshop participants could also deal more definitively with considerations on the scientific evaluation and indications for the technique and the future needs, if any, for a continuous registry for the technique. Inquiries about the Interim Registry and proposed workshop should be addressed to Dr. Michael B. Mock, Cardiac Diseases Branch, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20014.

The complexities and cost of conducting cardiovascular research and providing the best available care to the patients presenting with cardiac disease demand that the evaluation of any new or potentially promising technique, such as percutaneous transluminal coronary angioplasty, be conducted in a rational, scientific manner. They also call for a workable plan for translation of the scientific data base at both an appropriate time and appropriate manner to the medical community providing care for the patient.

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ANGINAL CHEST PAIN VERSUS ANGINA PECTORIS

In the recent report from the Framingham study on the remission of clinically diagnosed angina pectoris, Kannel and

Sorlie[1] demonstrated a different prognosis for two groups of patients with chest pain diagnosed as angina pectoris but failed to show in either group that the chest pain was due to ischemic heart disease. We believe that this is a critically important distinction in relation to prognosis and treatment because the real significance of the symptom of angina pectoris rests with its frequent (but not universal) association with the myocardial ischemia produced by significant coronary artery disease and the fact that specific forms of medical and surgical treatment are now available to treat the pathophysiologic state of myocardial ischemia. Although, as the authors have stated, angina pectoris can be assessed only subjectively, if the chest pain is due to myocardial ischemia this can be demonstrated objectively in most patients by treadmill exercise testing or radionuclide scanning and particularly by a combination of both.[2] When clinically indicated, coronary angiography can demonstrate the presence of anatomic lesions of the coronary arteries—that is, the presence of coronary artery disease, which is the most common, but not the only, cause of myocardial ischemia.

With such techniques so widely available at this time it is surely inadequate to diagnose one or more episodes of anginal chest pain as angina pectoris because of coexistent obesity, hypertension and an elevated serum cholesterol level. There are serious implications for the patient diagnosed as having a syndrome that carries the implication of coexistent ischemic heart disease in relation to work, life style, medical therapy and postulated future prognosis. We believe that these implications demand firmer confirmation of the diagnosis of ischemic heart disease. Previous angiographic studies of patients with a clinical diagnosis of typical angina pectoris have shown that patients can experience typical anginal symptoms (including a typical relation to exertion) in the presence of normal coronary arteries.[3–5]

The prognosis in the group of patients with the diagnosis of "transient angina pectoris" was that one would expect in patients without significant coronary artery disease and resembles that of previously described patients who had normal coronary arteries at angiography despite typical angina pectoris.[3–5] On the other hand, the patients with persistent angina had a prognosis more in keeping with the presence of significant coronary artery disease and clinically they more closely resemble the type of patient likely to be referred for coronary angiography and, possibly, surgery. Noteworthy was the 20 percent mortality rate in men with persistent angina over a 4 year period in the Framingham group,[1] which compares with an 11 percent mortality rate over 5 years in a large group of patients operated on for persistent angina secondary to angiographically proved coronary artery disease.[6]

We urge that the term angina pectoris be used only to describe the presence of specific *symptoms* secondary to objectively documented ischemic heart disease. Where documentation is lacking, perhaps a term such as anginal chest pain may be appropriate. If the fundamental *disease* is to be described, the terms coronary artery disease (to describe the pathology) or ischemic heart disease (to describe the pathophysiology) should be employed. The terms are not synonymous, and each one of these diagnoses carries quite different implications for the patient.

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REPLY

We agree that the term angina pectoris should signify only an ischemic type of chest pain. The designation of angina pectoris as due to coronary artery disease should probably require documentation by an exercise electrocardiogram or radionuclide scanning. It is clear that not all transient chest pain provoked by exertion is due to major occlusions of one or more coronary arteries.

However, the problem is rather complex. We cannot agree that these procedures, or even coronary angiography, settle the matter. In the final analysis, there is no escaping the fact that angina is a clinical syndrome or a pathophysiologic state and not an anatomic condition or an electrocardiographic abnormality provoked by exercise. We are sure that Lawrie and Morris have both seen on angiography severe coronary artery disease unaccompanied by any chest pain, as well as the converse. Likewise, many persons with blatantly positive electrocardiographic responses to exercise have no pain during the exertion or between tests. Conversely, not every patient who has angina on the treadmill has a positive electrocardiographic response. Furthermore, these discordant occurrences are not oddities, but rather frequent observations. According to Lawrie and Morris, we might have to give these another name as well—perhaps "silent angina."

Those characterized as having "angina pectoris" in the Framingham Study, particularly of the transient, remitting variety, may or may not have had coronary artery disease. The importance of the symptom of angina does indeed rest with its frequent association with myocardial ischemia produced by severe narrowing of the coronary arteries. It would be desirable for all subjects with suspected angina to have the diagnosis clarified by dynamic studies designed to demonstrate ischemia and deterioration of ventricular function under a load. This might in some cases relieve them of the burden of an unwarranted diagnosis of a potentially lethal illness that might undermine their faith in themselves or their future and affect their employment and insurance eligibility. This diagnosis should not be lightly bestowed on a patient.

Further diagnostic studies would also seem useful for those with persistent angina who are being considered for hazardous, costly or unpleasant medical or surgical remedies. Such studies are also useful to establish the amount of exercise that can be safely tolerated and to evaluate the prognosis for chest pain. For patients with persistent angina and a poor coronary risk profile the prognosis is so much like that of documented myocardial infarction that extensive diagnostic studies for diagnostic reasons alone would seem superfluous in most cases.

Lawrie and Morris find the 20 percent 4 year mortality rate in men with persistent angina worthy of comparison with the 11 percent mortality rate over 5 years observed in patients operated on for persistent angina despite lack of confirmation of the diagnosis in the former. The comparison is, of course,

inappropriate because there is no guarantee that the two samples are comparable in severity of underlying disease, or even in age. The patients in the Framingham study with angina, in contrast to the surgical series, are unselected as to number of vessels involved, heart size, left ventricular function or signs of cardiac failure. These factors are associated with greater mortality.

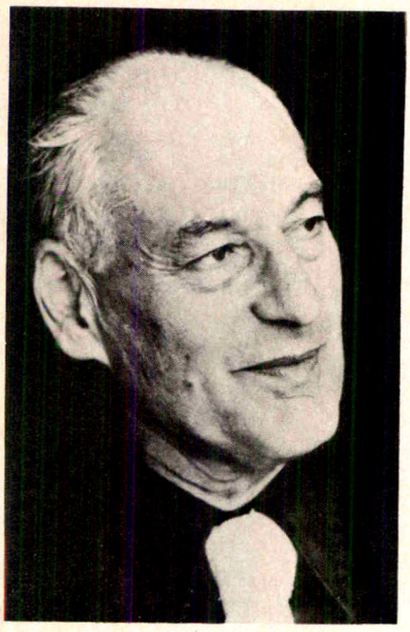
We do not know whether the proper conclusion from this study of the natural history of angina pectoris is that some "true angina" actually disappears and that when this occurs the prognosis is excellent or that when this happens another diagnosis should be considered. We think that both possibilities are likely. Unfortunately, in epidemiologic studies it is seldom feasible to carry out the more definitive studies required to probe the clues to pathogenesis uncovered. Lawrie and Morris may be in a position to do so and we strongly urge them to consider it.

Nevertheless, we believe the observations made are useful as they stand. It seems from this study that physicians should anticipate that a sizable proportion of their patients with angina will have a spontaneous remission. Also, it would seem ill advised to prescribe potentially hazardous medical or surgical remedies for transient angina without further information on the proper indications for therapy in this subgroup. What is clearly needed is a careful investigation of the underlying anatomy and pathophysiology to learn why a substantial amount of apparent angina disappears in both sexes and why this disappearance is associated with an excellent prognosis.

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President's Page:

Should We Reduce Graduate Cardiovascular Training Programs?



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In continuing the tradition of the "President's Page," I should like to preface it with a word of gratitude to the Editor of the Journal for a rare privilege afforded to the College President, to voice an opinion without being restricted by a subject matter, and without the restraining rigor of the Journal's peer review mechanism. Most privileges can be readily abused unless guarded by the recipient's sense of obligation. In this case, the obligation is to say something of interest to the membership and, if possible, to provide the reader with a stimulus for an exchange of views and ideas. I hope that my comments, which express my personal opinion because I have no time or opportunity to check my text in advance with the Board of Trustees or the appropriate committees of the College, will invite responses that I shall either answer personally or summarize within the text of ensuing "President's Pages.

The title of this "page" was provoked by the "Statement of Manpower" issued by the Federated Council for Internal Medicine on September 16, 1978.[1] The Council represents the prestigious organizations consisting of the American Board of Internal Medicine, the American College of Physicians, the American Society of Internal Medicine and the Association of Professors of Medicine. The limitations of space will permit me to give only a cursory account of this statement, but I trust that I will be able to convey faithfully the opinions of the Council and explain the roots of my negative reaction to their document.

I have no objection to the Council's statement in the preamble that "continuing efforts should be made to ensure that an appropriate number and distribution of internists are available for the provision of optimum medical care for the people of the United States." This is the reason why the Council has supported the National Study of Internal Medicine Manpower. Although the results of this study are not yet available, the Council is ready to identify the difficulty and make the appropriate recommendations for its solution. What is the actual problem? The National Study of Internal Medicine Manpower has shown that the number of trainees in subspecialty programs increased at a rate of about 11 percent per year during the past 6 or 7 years, and that the present overall 2:1 ratio of general internists to subspecialty internists could reverse in the next 20 years if the present numerical trend continues. The Council's statement does not make it clear how this calamity of substituting the subspecialty internist—who has acquired, in addition to the knowledge and experience common to the general internist, some special skills and interests—will detract from "the optimum medical care for the people of the United States." On the contrary, the Federated Council for Internal Medicine admits in its statement that most subspecialty internists now in practice deliver a substantial amount of primary care and that "delivery of primary care represents a significant proportion of the subspecialists' professional activities."

Leaving this issue unresolved, the Council presents observations and conclusions concerning "the importance of an appropriate distribution of manpower within internal medicine, including a proper balance between general internists and subspecialty internists." As an internist, I strongly believe that the profession of internal medicine is challenging, mind-expanding, humanitarian and beneficial to the welfare of the human race. I also expect that members of other medical specialties have similar beliefs about their own professions. But I am afraid that efforts to create "an appropriate distribution" or a "proper balance" between different specialists or subspecialists within a specialty must require some form of coercion or manipulation, which is difficult to achieve without abridging the freedom of personal choice.

Unusual circumstances may force society to curtail or suspend privileges of certain groups or individuals, but the Council does not make a good case for such an action in this instance. It claims that "the overall rate of increase in numbers of subspecialty trainees has been excessive" and suggests that "reimbursement levels" for technical procedures "very significantly influence career choices among internal medicine trainees." This prompts the Council to state that "an increased emphasis on training in general internal medicine would be in the public interest."

These are strange notions, indeed. I wonder who among the Council's members will summon up the courage to approach a third year medical resident preparing to spend additional (usually at least

two) years in a teaching hospital in order to acquire the knowledge and the skill required to practice the specialty of adult or pediatric cardiology, and tell him or her that such action is not in the best public interest because it amounts to seeking higher levels of reimbursement for technical procedures.[1] And what might be the reply to the anticipated countering questions: Why is my increased knowledge, experience and competence not in the public interest? Why is it wrong to be motivated by the prospect of higher reimbursement levels? Why should the knowledge and the technical skills remain the undisputed domain of a group limited to few selected competitors?

The last part of the Council's statement entitled "Recommendations" is not surprising, in view of the previously expressed opinions. The Council recommends adjusting the number of clinical subspecialty training positions "to meet health care needs in the United States where appropriate," and it instructs the chairpersons of departments of medicine and directors of internal medicine training programs to modify, limit or reduce the number of clinical subspecialty slots. At the same time, it states that "the number of general internists should be increased," and their training "should place reduced dependence on technical procedures and a greater emphasis on bedside skills and clinical judgment." While the nostalgia for the allegedly vanishing "bedside skills" cannot be dismissed lightly, the methodology of reducing the dependence on technical procedures may pose some interesting logistic problems. For instance, I can envision a scenario in which the resident is denied an electrocardiograph until he figures out from the intensity of the heart sounds whether tachycardia is supraventricular or ventricular, or perhaps is kept away from the echocardiograph before he masters the art of percussing a pericardial effusion. But the impact of technology on medical practice is a separate subject that is beyond the scope of this "page."

The statement of the Federated Council for Internal Medicine ends with a pronouncement that "further data are needed to develop a coherent national policy regarding appropriate numbers of medical students, general internists and other primary care physicians and subspecialists of various types." This is probably the most significant part of the statement because it is an admission of a need for the appropriate data and an expression of hope that some appropriate information will be developed by the National Study of Internal Medicine Manpower.

All of us will undoubtedly follow with interest the national manpower study and the results of other future manpower studies, but we must not forget the efforts of the American College of Cardiology to obtain the needed data. In 1973, the College, aided by a contract from the National Heart and Lung Institute and helped by the consultants representing the American Heart Association, American College of Chest Physicians and Subspecialty Board in Cardiovascular Disease, prepared an extensive evaluation of cardiology training and manpower requirements edited by Forest H. Adams and R. C. Mendenhall.[2] From this report, we learn that in 1973 we had 177 physicians per 100,000 population, while the number of cardiologists averaged 5.6 per 100,000 population. The cardiologists were physicians who estimated that they had spent 50 percent or more of their professional time providing care for patients with cardiac problems. About 50 percent of all cardiologists were certified in Internal Medicine and 10 percent certified in Cardiovascular Disease.

Does this represent an adequate number of cardiologists needed in the country? The report wisely does not attempt to answer this question, but provides precise data relating to the number of new trainees needed to maintain the present ratio of about six cardiologists per 100,000 population. The report also lists some of the factors that could contribute to the increasing need for cardiologists. These include improving standard of care, development of new diagnostic and surgical techniques and the recently imposed restriction on numbers of foreign graduates entering the country. We must also consider the possible changes in the prevalence of heart disease. The present estimate is that 24.9 percent of the adult American population have definite or suspected heart disease.[2]

It is obvious that we do not know how many general internists and how many cardiologists are needed for the optimal medical care in this country. My preference would be to see the issue determined by the process of self-regulation based on the laws of supply and demand. When the prospective cardiologists receive word that the previous graduates of cardiology training programs face problems in their practice that require no special skills, they may choose to terminate their own training at an earlier stage and embark on the practice of general internal medicine. It would be a gross oversimplification to assume that pure pragmatism is the sole power motivating human actions. The quest for new knowledge, the intellectual curiosity, the joy and pride in mastering new skills may represent a much stronger motivation than the prospects of marketability or even the prestige of Board certification.

In the final analysis, it is as appropriate for the Federated Council for Internal Medicine to be concerned about the status of the general internist as it is appropriate for the American College of Cardiology to be concerned about the status of the cardiologist. However, as citizens and physicians, we all should take under advice the following statement from the Physician Manpower report of the American Medical Association adopted in June 1978: "The public can best be served under an educational system which maximizes the freedom of individuals to choose and develop their career interests and opportunities under normal competitive conditions. This applies to both the selection of medicine as a career and the choice of speciality."[3]

Borys Surawicz, MD, FACC
President
American College of Cardiology

References

1. Statement on Manpower. Federated Council for Internal Medicine, Forum on Medicine, November 1978, p 20–21
2. Report of an Evaluation of Cardiology Training and Manpower Requirements (Adams FH, Mendenhall RC, ed). DHEW Publication no. (NIH) 74-623
3. Physician Manpower Medical Education, II. A report of the American Medical Association, June 1978

NEW MEMBERS

The following individuals were elected to membership in the American College of Cardiology on November 30, 1978 in the category indicated.

FELLOWSHIP

AHMAD, Salahuddin, MBBS, Granite City, IL
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YOUNAN, Kivarkis Y., MD, Parlin, NJ

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning, Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

APRIL 1979 THROUGH JULY 1979

Month/Dates	Course Director	Title of Program
April 2–4	Samuel Kaplan, MD, FACC	**Non-invasive Pediatric Cardiology**
April 5–7	John A. Spittell, Jr., MD, FACC	**Peripheral Vascular Disease**
April 9–11	Keith E. Cohn, MD, FACC	**Exercise Testing**
April 18–20	J. O'Neal Humphries, MD, FACC	**Coronary Care Units—15 Years Later**
April 23–25	Arthur E. Weyman, MD, FACC	**Cross-sectional Echocardiography**
April 26–28	Robert G. Tancredi, MD, FACC	**Pulmonary, Renal and Electrolyte Considerations in Cardiovascular Disease**
May 3–5	Daniel S. Berman, MD, FACC	**Nuclear Cardiology**
May 7–9	Leonard S. Dreifus, MD, FACC	**Cardiac Rehabilitation: Principles and Techniques**
May 14–16	Louis Lemberg, MD, FACC Agustin Castellanos, Jr., MD, FACC	**CCU Update for Nursing Supervisors**
May 21–23	James E. Doherty, III, MD, FACC	**Clinical Cardiovascular Pharmacology: Rational Approach to Drug Therapy**
May 24–25	Joseph K. Perloff, MD, FACC	**The Fundamentals of Echocardiography: A Practical Course for Clinicians**
May 30–June 1	Ira H. Gessner, MD, FACC	**The Principles of Pediatric Cardiology: A Fundamental Approach**
June 4–6	G. Charles Oliver, MD, FACC	**Ambulatory Monitoring and Sudden Death**
June 11–13	Shahbudin H. Rahimtoola, MD, FACC	**Valvular Heart Disease**
June 20–22	Michael S. Gordon, MD, FACC	**Cardiac Auscultation**

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Leonard S. Dreifus, MD, FACC
Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

APRIL 1979 THROUGH AUGUST 1979

To be arranged individually — **Preceptorships in Cardiology.** Arthur Seizer, FACC, director. Pacific Medical Center, San Francisco, Calif.

APR. 2–6 — **Consultant's Course in Cardiology.** Michael V. Herman, FACC, director and Richard Gorlin, FACC, Simon Dack, FACC and Louis E. Teichholz, FACC, co-directors. Mount Sinai Medical Center, New York, NY

APR. 2–11 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 3–4 — **Management of the Patient Who Has Survived Acute Myocardial Infarction.** Sylvan L. Weinberg, FACC, director. Stouffer's Dayton Plaza Hotel, Dayton OH

APR. 19–21 — **New Diagnostic and Therapeutic Approaches in Cardiology 1979.** Edmund H. Sonnenblick, FACC and James Scheuer, FACC, directors. Plaza Hotel, New York, NY

APR. 24–27 — **Cardiac Arrhythmias: Recognition, Electrophysiology and Treatment.** John A. Kastor, FACC and Mark E. Josephson, FACC, co-directors. University City Holiday Inn, Philadelphia, PA

APR. 26–28 — **Myocardial Infarction and Other Ischemic Heart Syndromes.** C. Richard Conti, FACC, director and Carl J. Pepine, FACC and Leonard G. Christie, co-directors. Innisbrook Resort and Golf Club, Tarpon Springs, FL

MAY 3–5 — **Critical Care Cardiology.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. Golden Gateway Holiday Inn, San Francisco, CA

MAY 3–5 — **Ischemic Heart Disease.** James E. Dalen, FACC, director and Thomas J. Ryan, FACC, Thomas W. Smith, FACC, Herbert J. Levine, FACC and Joseph S. Alpert, FACC, co-directors. Copley Plaza Hotel, Boston, MA

MAY 9–11 — **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, Antonio C. de Leon, Jr., FACC, and John F. Stapleton, co-directors. Georgetown University Medical Center, Washington, DC

MAY 18–21 — **A Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC, and Leo Schamroth, FACC, directors. Sheraton Sand Key Hotel, Clearwater Beach, FL

MAY 21–24 — **Coronary Atherosclerotic Heart Disease—1979.** J. Willis Hurst FACC, director and Robert C. Schlant, FACC, co-director. Colony Square Hotel, Atlanta, GA

JUNE 8–10 — **Cardiac Auscultation Workshops.** Jules Constant, FACC, director. Niagara Hilton Hotel, Niagara Falls, NY

JUNE 13–16 — **Sixth Annual Symposium. Clinical Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** Arthur D. Hagan, FACC, director and William F. Friedman, FACC and Walter V. R. Vieweg, FACC, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

JUNE 21–23 — **Medical and Surgical Management of Coronary Artery Disease.** M. Leo Hughes, Jr., FACC, director and Robert C. K. Riggins and Richard P. Anderson, co-directors. Virginia Mason Medical Center, Seattle, WA

JUNE 21–23 — **Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** Arthur D. Hagan, FACC, director and Walter V. R. Vieweg, FACC and Joel S. Karliner, FACC, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

AUG. 25–27 — **Tutorials in the Tetons: Cardiac Emergencies (Fifth Annual).** Robert S. Eliot, FACC and Alan D. Forker, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Moran, WY

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- Arrange the paper in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- Number all pages in above sequence, beginning with title page as 1, abstract as 2, etc.
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- Add at end of abstract: list of 2 to 6 key words and subjects for indexing.

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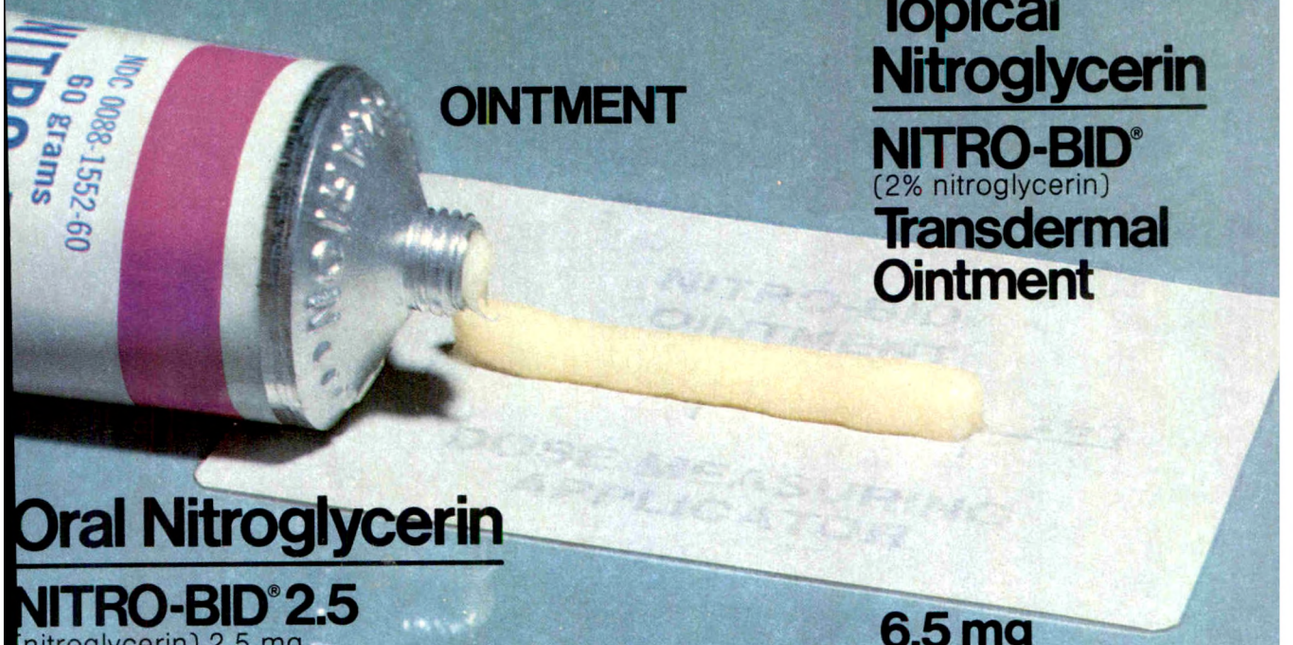
28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

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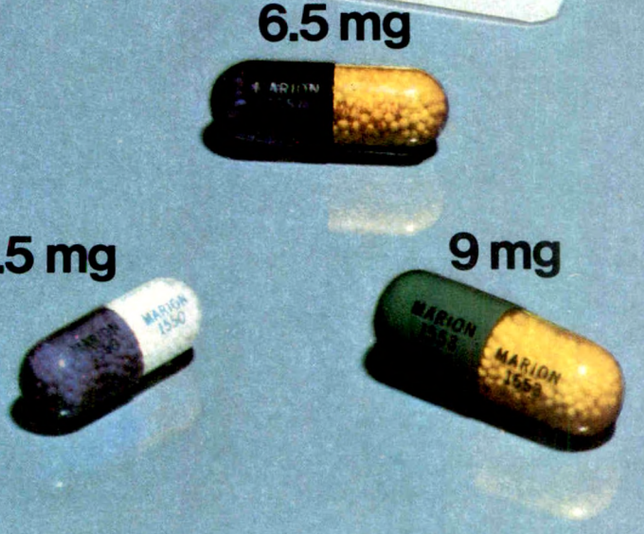
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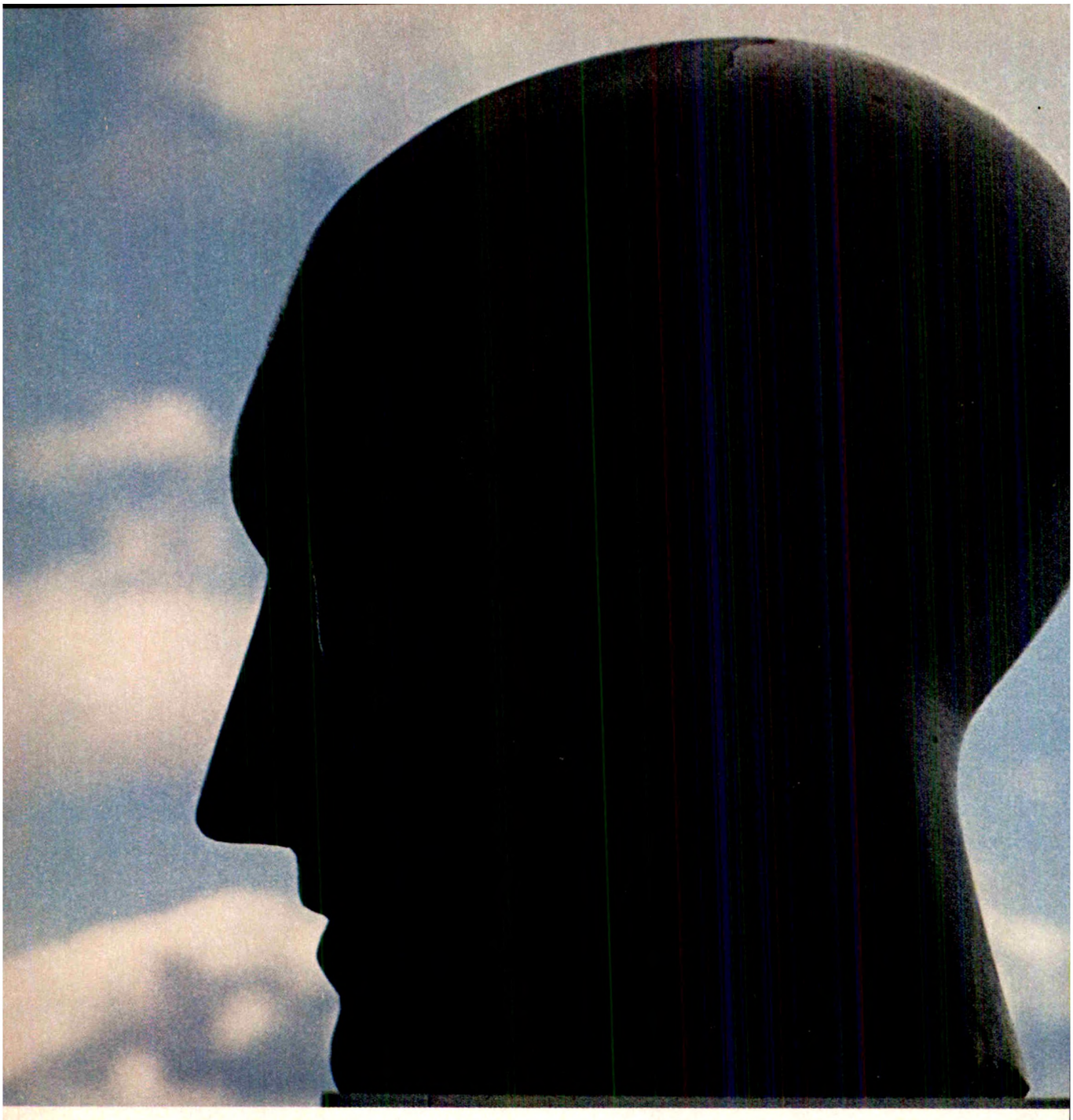
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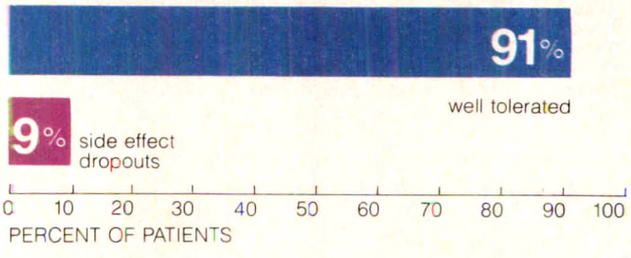
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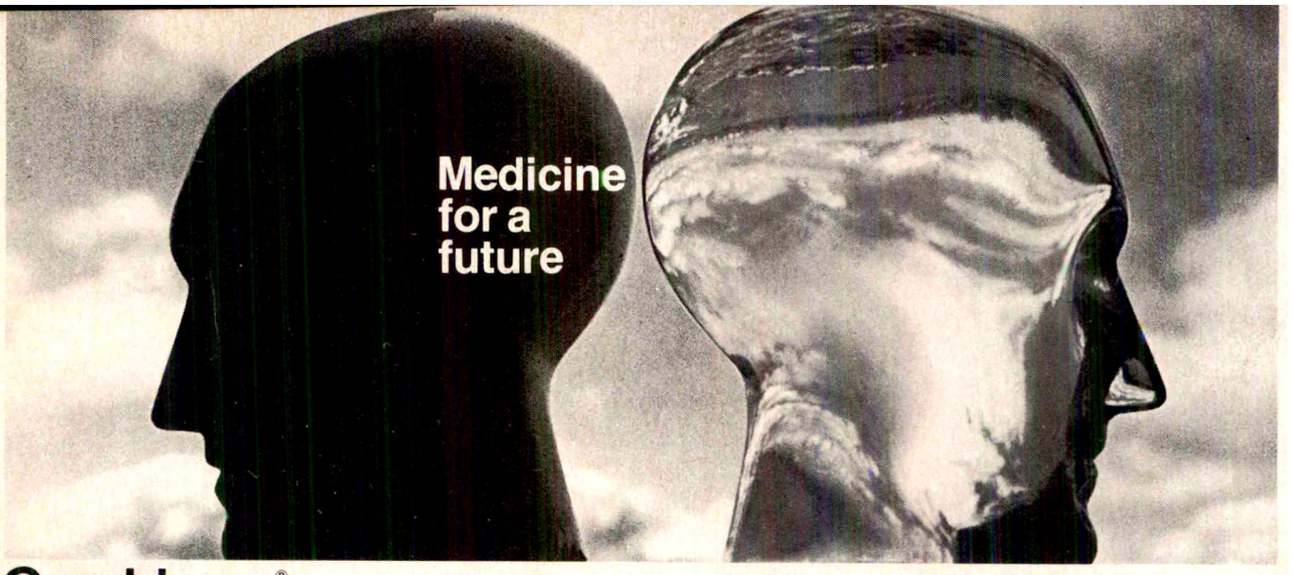
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Please see brief summary of the prescribing information on the last page of this ad for warnings, precautions, and adverse reactions.

*Orthostatic hypotension has been reported with chlorthalidone and may be potentiated when chlorthalidone is combined with alcohol, barbiturates, or narcotics.



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Each tablet contains: Catapres* (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component.This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave, ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres* 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres* 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

References:

1. Data on file at Boehringer Ingelheim Ltd.
2. Pettinger WA: NEJM, 293:1179, 1975.
3. Katz FH: Hosp Med, 13:34, 1977.

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Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects, ventricular premature beats, ventricular tachycardia or flutter while on the drug.

Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances. 101-71

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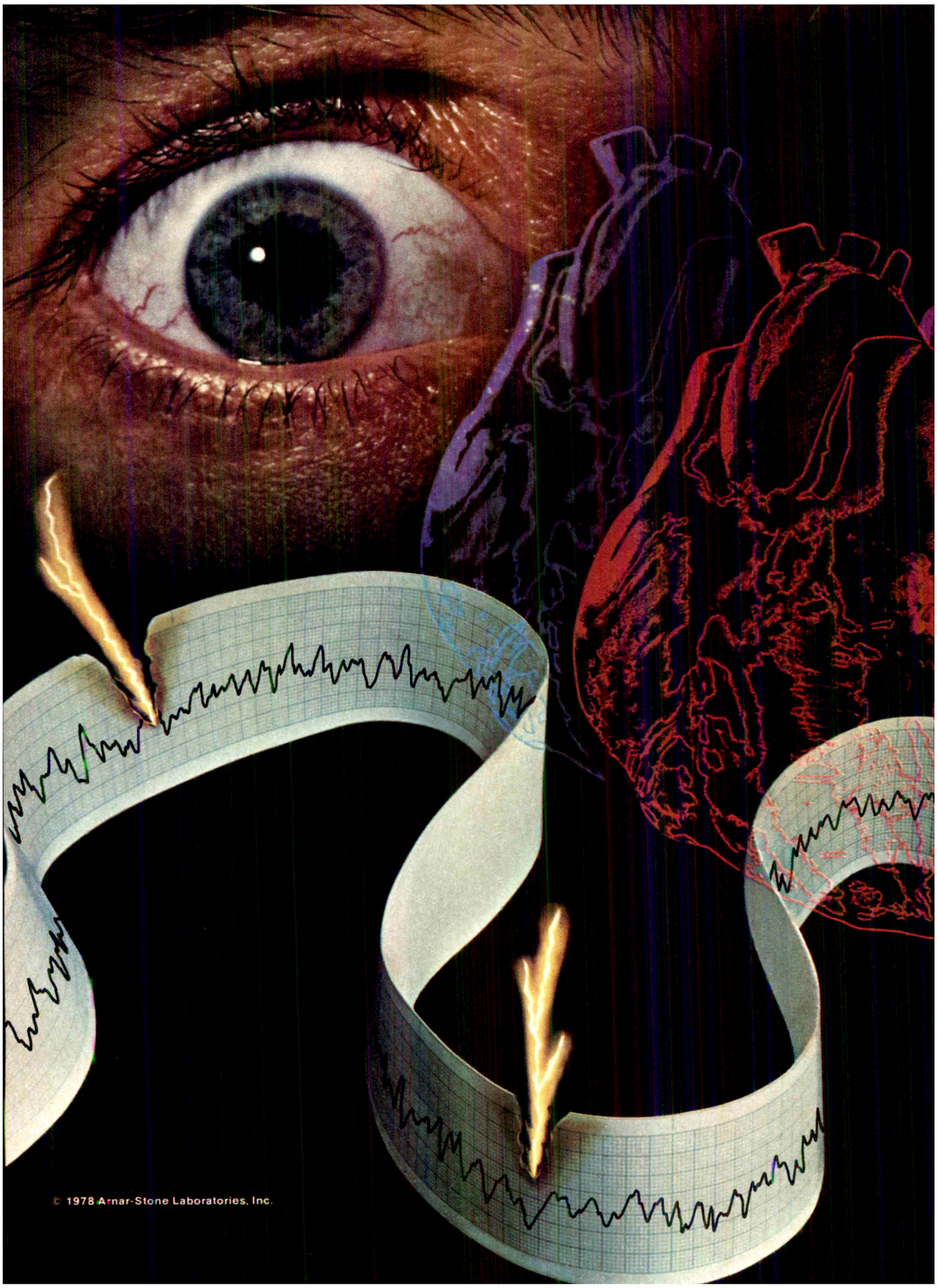
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Not meant to imply time relationship between administration of Bretylol and patient response.

BRETYLOL® (bretylium tosylate) is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to first-line therapy.

At present, Bretylol should not be considered a first-line antiarrhythmic agent. Use of Bretylol should be limited to facilities where equipment for constant monitoring of arrhythmias is available.

BRETYLOL® bretylium tosylate

BRETYLOL: in ventricular fibrillation

In reported clinical situations, BRETYLOL® (bretylium tosylate) was effective in conjunction with electrical cardioversion, even in patients refractory to other antiarrhythmic therapies. BRETYLOL raised the ventricular fibrillation threshold in animal studies. Suppression of ventricular fibrillation usually occurs within minutes following intravenous administration, the effect generally lasting 6 to 8 hours.

BRETYLOL: in ventricular tachycardia

In clinical studies, BRETYLOL was effective in the management of ventricular tachycardia and other ventricular ectopic rhythms, even those recurrent and refractory to existing antiarrhythmic therapies. Clinical benefits can usually be observed 20 minutes or more following parenteral administration with duration of action 6 to 8 hours.

BRETYLOL: effects on cardiac function

Unlike other antiarrhythmic drugs, BRETYLOL has demonstrated (in animal studies) a positive inotropic effect on the myocardium and did not significantly decrease A-V conductivity. In man, BRETYLOL generally did not depress myocardial function and maintained cardiac output. These effects may be due to release of norepinephrine from nerve terminals, potentiation of the effects of endogenous catecholamines and/or a direct action on the myocardium.

BRETYLOL: contraindications/adverse reactions

There are no contraindications for BRETYLOL in the treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

The principal adverse reaction is hypotension, usually postural. This is due to reduction of peripheral vascular sympathetic tone, *not* to depression of myocardial function.

Due to the initial release of norepinephrine from the adrenergic postganglionic terminals, there may be initial *transient* increases in blood pressure, heart rate and/or PVC's. These generally return promptly to preadminist tion levels.

Nausea and vomiting can usually be obviated by t slow intravenous administration of a dilute solution BRETYLOL.

For a full description of adverse reactions, please re to the complete prescribing information on the last pa of this advertisement.

Bretylol Clinical Studies

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Bernstein, J.G. and Koch-Weser, J. Effectiveness of bretylium tosyl against refractory ventricular arrhythmias. *Circulation.* 45:1024-10 1972. (Reference No. 2)

Cohen, H.C., Gozo, E.G., Langendorf, R., Kaplan, B.M., Chan, A., Pick, and Glick, G. Response of resistant ventricular tachycardia to bretyli *Circulation.* 47:331-340, 1973. (Reference No. 3)

Chatterjee, K., Mandel, W.J., Vyden, J.K., Parmley, W.W. and Forrest J.S. Cardiovascular effects of bretylium tosylate in acute myocard infarction. *JAMA.* 223:757-760, 1973. (Reference No. 5)

Dhurandhar, R.W., Teasdale, S.J. and Mahon, W.A. Bretylium tosylate the management of refractory ventricular fibrillation. *Can. Med. Assoc. 105*:161-166, 1971. (Reference No. 7)

Sanna, G. and Arcidiacono, R. Chemical ventricular defibrillation of human heart with bretylium tosylate. *Am. J. Cardiol.* 32:982-987, 19 (Reference No. 9)

Bretylol Pharmacological Studies

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Bacaner, M. Quantitative comparison of bretylium with other antifib latory drugs. *Am. J. Cardiol.* 21:504-512, 1968. (Reference No. 13)

Cardinal, R. and Sasyniuk, B.I. Electrophysiological effects of bretyli tosylate on subendocardial Purkinje fibers from infarcted canine hear *J. Pharmacol. Exp. Ther.* 204:159-174, 1978. (Reference No. 17)

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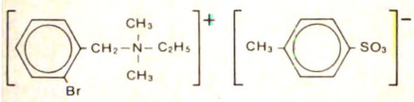
BRETYLOL® bretylium tosylate

BRETYLOL INJECTION

FOR INTRAMUSCULAR OR INTRAVENOUS USE

DESCRIPTION

BRETYLOL (bretylium tosylate) is o-Bromobenzyl ethyldimethylammonium p-toluene sulfonate. The chemical structure is:



$C_{18}H_{24}BrNO_3S$ Mol. Wt. 414.39

BRETYLOL is a white, crystalline powder with an extremely bitter taste. It is freely soluble in water and alcohol. Each ml of sterile, pyrogen-free solution contains 50 mg bretylium tosylate in Water for Injection, USP. The pH is adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. BRETYLOL contains no preservative.

CLINICAL PHARMACOLOGY

BRETYLOL (bretylium tosylate) is a bromobenzyl quaternary ammonium compound which selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.

BRETYLOL also suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of BRETYLOL are not established. In efforts to define these mechanisms, the following electrophysiologic actions of BRETYLOL have been demonstrated in animal experiments:

1. Increase in ventricular fibrillation threshold.

2. Increase in action potential duration and effective refractory period without changes in heart rate.

3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, BRETYLOL restores these parameters toward normal.

4. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular induction velocity.

The restoration of injured myocardial cell electrophysiology toward normal,

(Prescribing Information continued below)

In various studies of BRETYLOL excretion, estimates of the terminal half-life have varied from about 5 to about 10 hours, with an even wider range in individual subjects (4 to 17 hours). Whether this represents true intrapatient variability or limitations of methodology remains to be determined.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when BRETYLOL is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of BRETYLOL to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index, and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS

BRETYLOL is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine or procainamide. At this time, BRETYLOL should not be considered a first-line antiarrhythmic agent.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS

There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS

1. Hypotension: Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, light-headedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

(Prescribing Information continued below)

ular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

2. Use Various Sites for Intramuscular Injection: When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL is excreted principally via the kidney, dosage should be reduced in patients with impaired renal function.

ADVERSE REACTIONS

Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

DOSAGE AND ADMINISTRATION

BRETYLOL is to be used clinically only for treatment of life-threatening ventricular arrhythmias under constant electrocardiographic monitoring. Since there is a delay in onset of its antiarrhythmic action, BRETYLOL is not to be considered or used as a replacement for rapidly-acting antiarrhythmic agents currently in use. The clinical use of BRETYLOL is for short-term use only. Patients should either be kept supine during the course of BRETYLOL therapy or be closely observed for postural hypotension. The optimal dose schedule for parenteral administration of BRETYLOL has not been determined. There is comparatively little experience with dosages greater than 30 mg/kg/day, although such doses have been used without apparent adverse effects. The following schedule is suggested:

A. For Immediately Life-threatening Ventricular Arrhythmia, as in Ventricular Fibrillation: Administer undiluted BRETYLOL at a dosage of 5 mg/kg of body weight by rapid intravenous injection. Other usual cardiopulmonary resuscitative procedures, including electrical cardioversion, should be employed prior to and following the injection in accordance with good medical practice. If ventricular fibrillation persists, the dosage may be increased to 10 mg/kg and repeated at 15 to 30 minute intervals until a total dose of not more than 30 mg/kg of body weight has been given. For maintenance dosage, see below.

B. Other Ventricular Arrhythmias:

1. Intravenous Use: *BRETYLOL must be diluted as follows before intravenous administration:* Using aseptic technique, dilute contents of one BRETYLOL ampul (10 ml containing 500 mg bretylium tosylate) to a minimum of 50 ml with Dextrose Injection, USP or Sodium Chloride Injection, USP.

Administer the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg of body weight by intravenous infusion over a period greater than 8 min-

(Prescribing Information continued below)



s well as the increase of the action potential duration and effective refractory eriod without changing their ratio to each other, may be important factors in uppressing re-entry of aberrant impulses and decreasing induced dispersion f local excitable states.

BRETYLOL induces a chemical sympathectomy-like state which resemles a surgical sympathectomy. Catecholamine stores are not depleted by RETYLOL, but catecholamine effects on the myocardium and on peripheral ascular resistance are often seen shortly after administration because RETYLOL causes an early release of norepinephrine from the adrenergic ostganglionic nerve terminals. Subsequently, BRETYLOL blocks the reease of norepinephrine in response to neuron stimulation. Peripheral adenergic blockade regularly causes orthostatic hypotension but has less ffect on supine blood pressure. The relationship of adrenergic blockade to he antifibrillatory and antiarrhythmic actions of BRETYLOL is not clear. In a tudy in patients with frequent ventricular premature beats, peak plasma oncentration of BRETYLOL and peak hypotensive effects were seen within he hour of intramuscular administration, presumably reflecting adrenergic euronal blockade. However, suppression of premature ventricular beats was ot maximal until 6-9 hours after dosing, when mean plasma concentration ad declined to less than one-half of peak level. This suggests a slower echanism, other than neuronal blockade, was involved in suppression of e arrhythmia. On the other hand, antifibrillatory effects can be seen within inutes of an intravenous injection, suggesting that the effect on the yocardium may occur quite rapidly.

BRETYLOL has a positive inotropic effect on the myocardium, but it is ot yet certain whether this effect is direct or is mediated by catecholamine elease.

BRETYLOL is eliminated intact by the kidneys. No metabolites have been entified following administration of BRETYLOL in man and laboratory anials. In man, approximately 70 to 80% of a ^{14}C-labelled intramuscular dose excreted in the urine during the first 24 hours, with an additional 10% creted over the next three days.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY

The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

USE IN CHILDREN

The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

PRECAUTIONS

1. Dilution for Intravenous Use: BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventric-

utes. More rapid infusion may cause nausea and vomiting. A second dose may be given in 1 to 2 hours if the arrhythmia persists.

2. For Intramuscular Injection: (*Do not dilute BRETYLOL prior to intramuscular injection.*) Inject 5 to 10 mg BRETYLOL per kg of body weight. Dosage may be repeated in 1 to 2 hours if the arrhythmia persists. Thereafter maintain with same dosage every 6 to 8 hours.

Intramuscular injection should not be made directly into or near a major nerve, and the site of injection should be varied on repeated injection.

C. Maintenance Dosage: The diluted BRETYLOL solution may be administered by intermittent bolus infusion or by constant infusion.

1. Intermittent Infusion: Infuse the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg body weight, over a period greater than 8 minutes, every 6 hours. More rapid infusion may cause nausea and vomiting.

2. Constant Infusion: Infuse the diluted solution at a dosage of 1 to 2 mg BRETYLOL per minute.

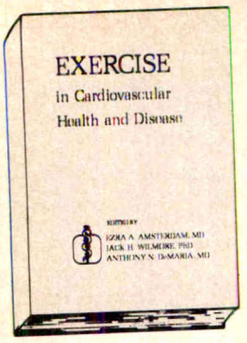
Dosage of BRETYLOL should be reduced and discontinued in 3 to 5 days under electrocardiographic monitoring. Other appropriate antiarrhythmic agents should be substituted, if indicated.

HOW SUPPLIED

NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP. pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, pyrogen-free. July 1978

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Jack H. Wilmore, PhD, Professor and Head Dept. of Physical Education & Athletics, Univ. Arizona
Anthony N. DeMaria, MD, Dir. Echocardiography Section, Univ. of Calif. School of Medicine

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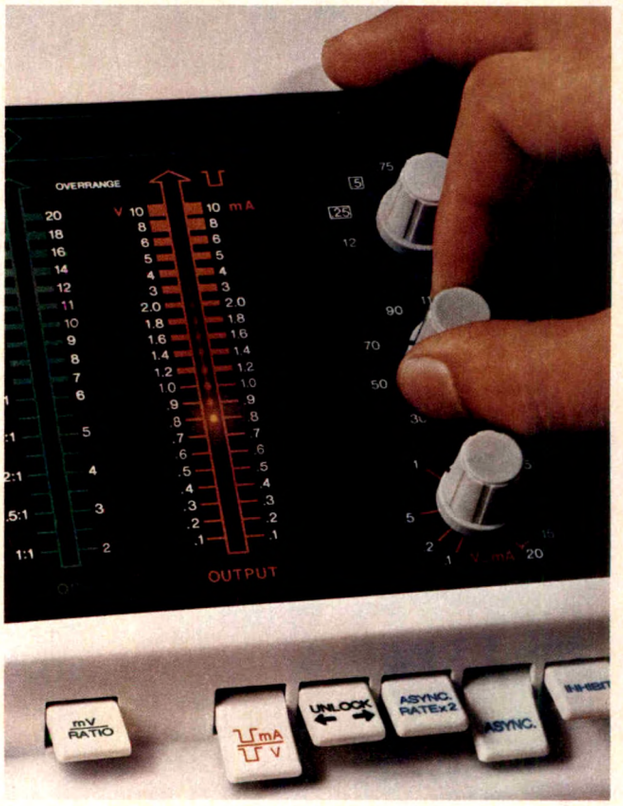
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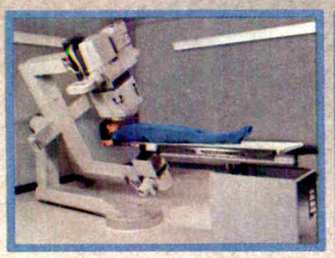


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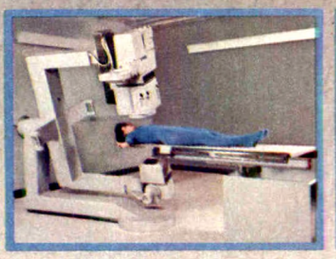
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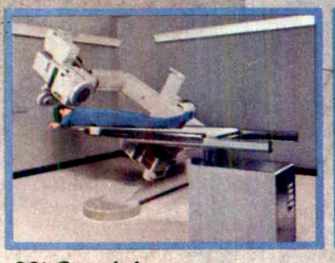
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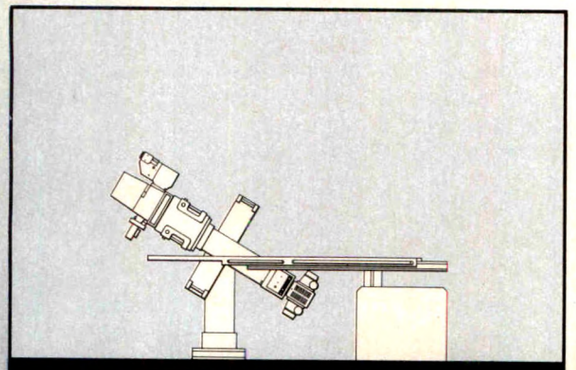


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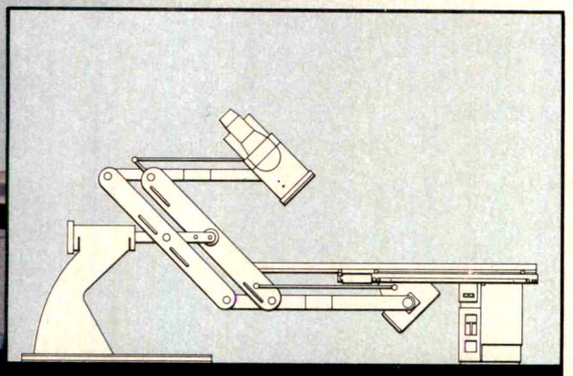
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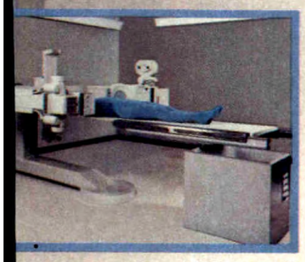
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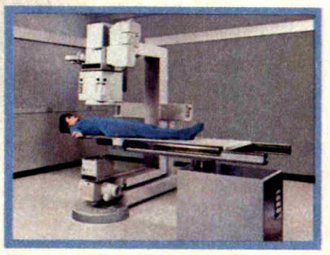
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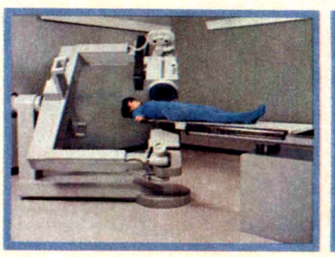
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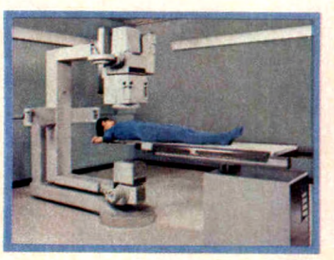
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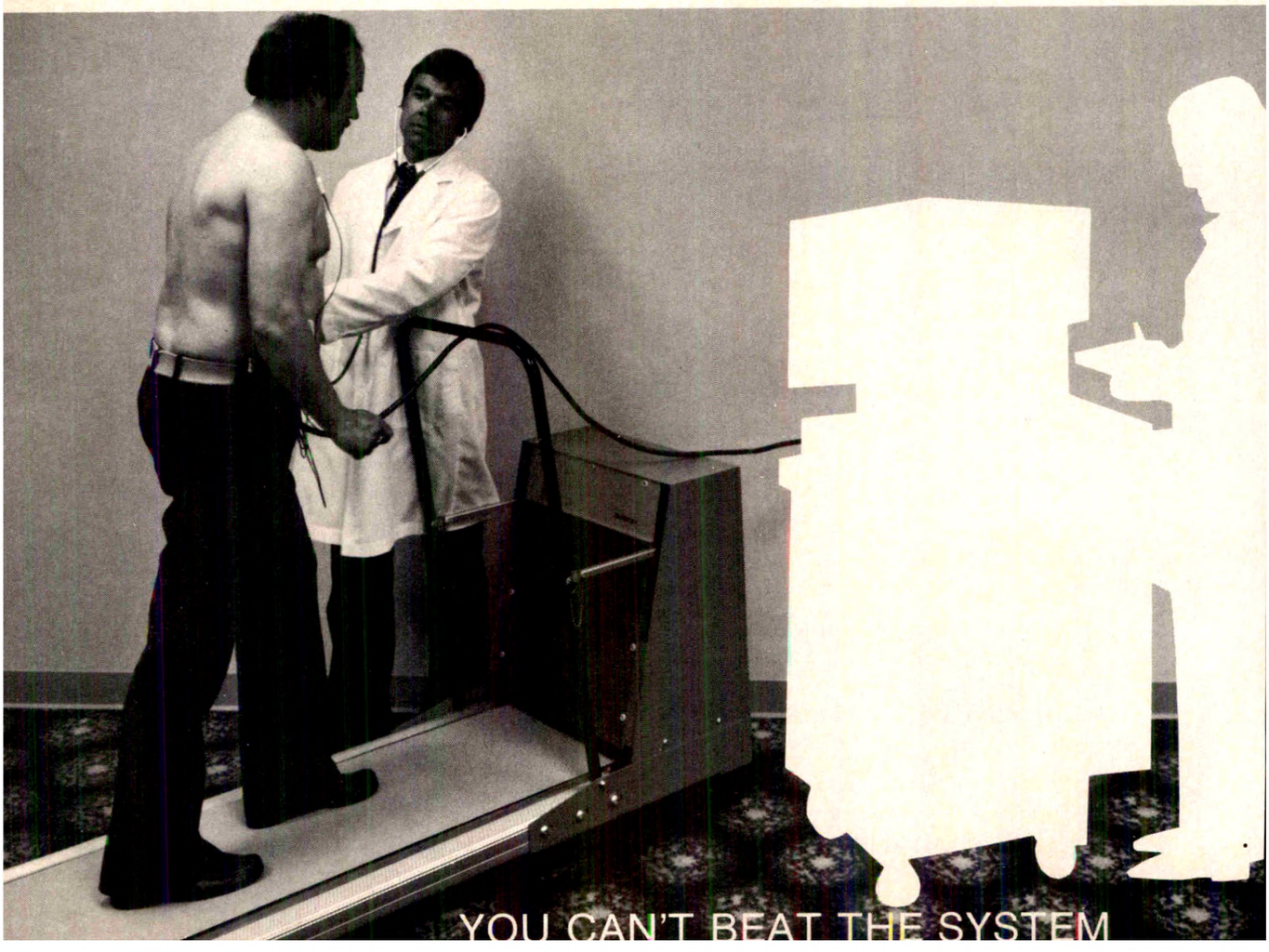
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Caribe Hotel, San Juan, Puerto Rico
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Credit: 20.5 Hrs. AMA Category I; AAFP Prescribed; FMA Prescribed; ACEP Category I
Director: Henry J.L. Marriott, M.D., St. Petersburg, Florida

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July 28 - 31, 1979
Edmonton, Alberta
Fee: $125.00
Credit: 24 hrs. AMA Category I, AAFP Prescribed; ACEP Category I Topics: Electrophysiology, Diagnosis and Treatment of Arrhythmias and Blocks
Faculty: Henry J.L. Marriott, M.D., St. Petersburg, Florida
Jody Decker, R.N., Toronto, Ontario

17th ANNUAL SEMINAR IN CARDIOLOGY

September 4 - 11, 1979
London, England
Fee: $200.00
Credit: 24 Hrs. AMA Category I; AAFP Prescribed; ACEP Category I; Selected Topics in Cardiology
Faculty: International
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Dr. Desmond Julian, Newcastle England
Dr. Henry J.L. Marriott, St. Petersburg, Florida
Dr. Neil Moore, Philadelphia, Pennsylvania
Dr. Demetrio Sodi-Pallares, Mexico City, Mexico
Dr. Jack Spittell, Rochester, Minnesota
Dr. Edward Swanick, St. Petersburg, Florida
Dr. Louis Teichholz, New York City, New York
Dr. Hein J. J. Wellens, Maastricht, The Netherlands

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October 4 - 8, 1979
Clearwater Beach, Florida
Fee: $100.00
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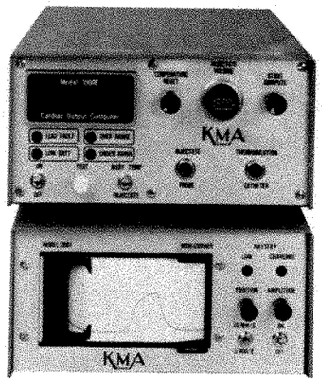
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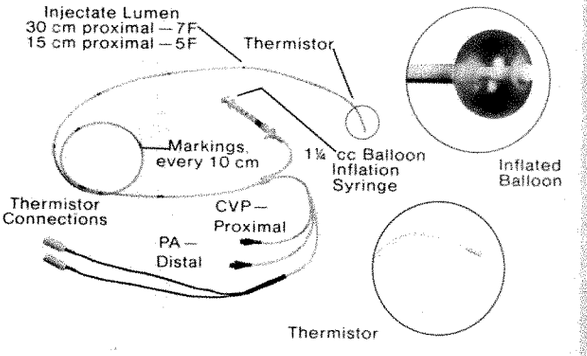
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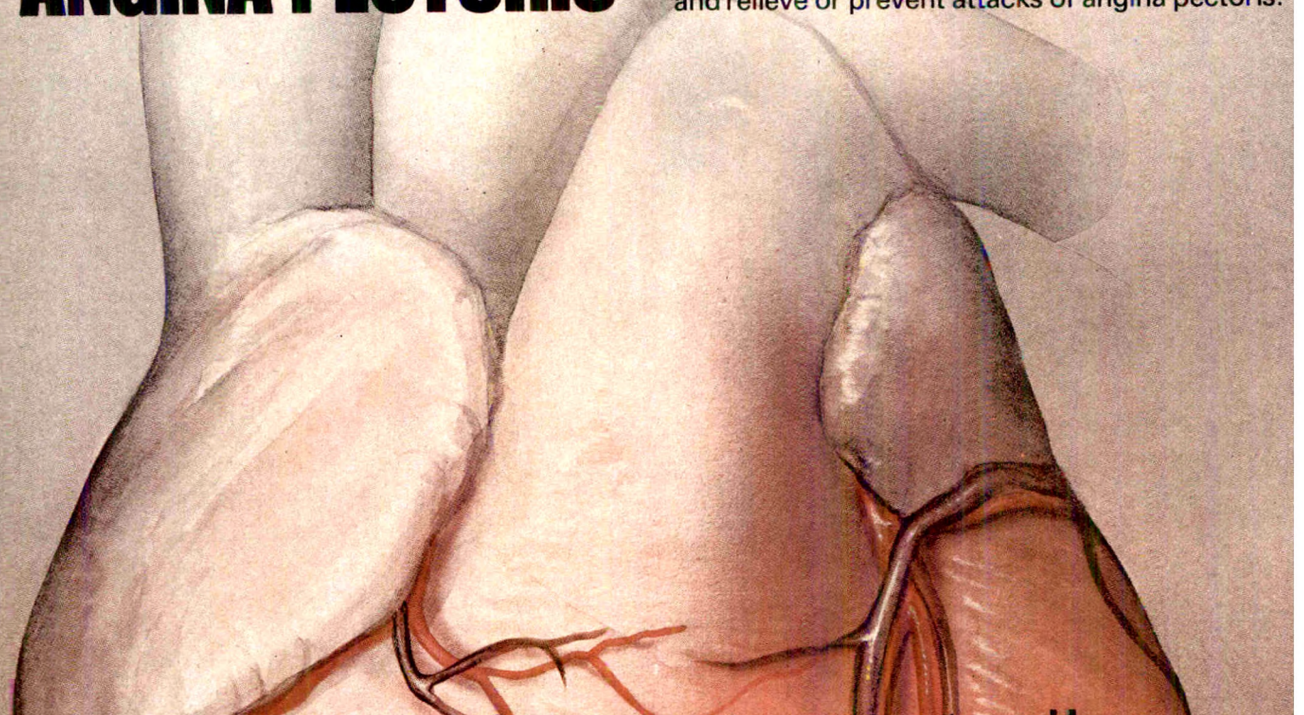
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HELPS THE HEART IN THE CONTROL OF ANGINA PECTORIS*

The established use of Isordil in the management of angina pectoris for more than two decades has often been ascribed only to the vasodilatation it produces in the coronary arteries. Recent investigations, however, suggest that an even more important effect of this agent is to dilate peripheral arteries and veins. Arterial dilatation lowers impedance to left ventricular ejection, reducing afterload. Venous dilatation leads to venous pooling and a fall in right and left ventricular filling pressure, thus reducing preload.

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to abort or prevent acute angina attacks

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***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

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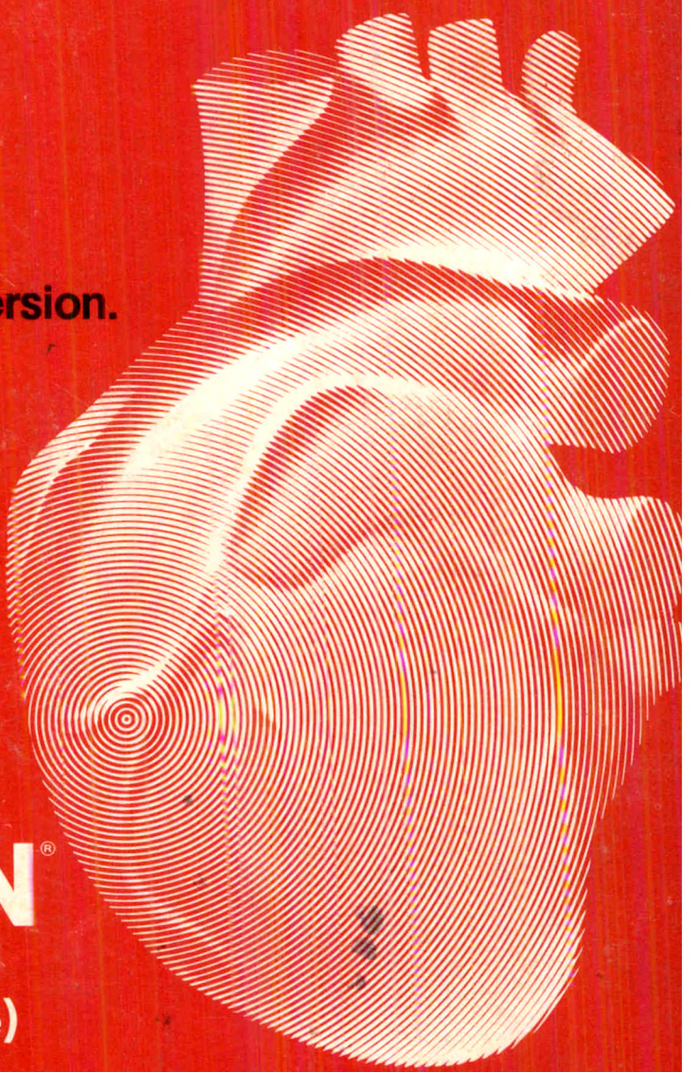
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CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm —whether with CARDIOQUIN Tablets or electroconversion— only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

Purdue Frederick

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MAY 1979

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The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Unstable Angina and Intraaortic Balloon

Recent Advances in Digitalis Research

Surgery for Asymptomatic Coronary Artery Disease

Contents on Page A6

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TABLETS: 500 mg, 250 mg, and 125 mg

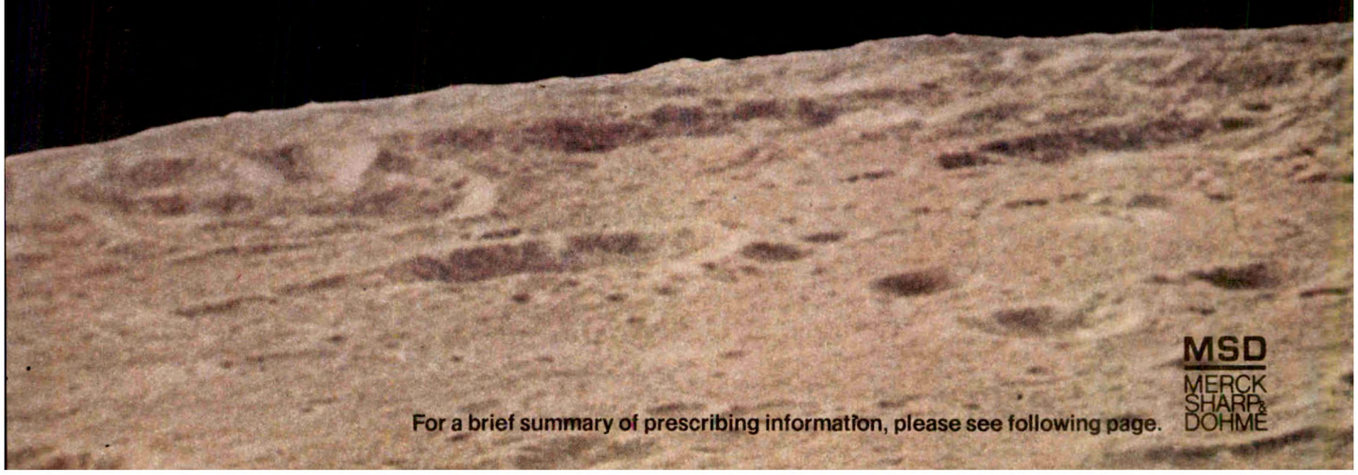
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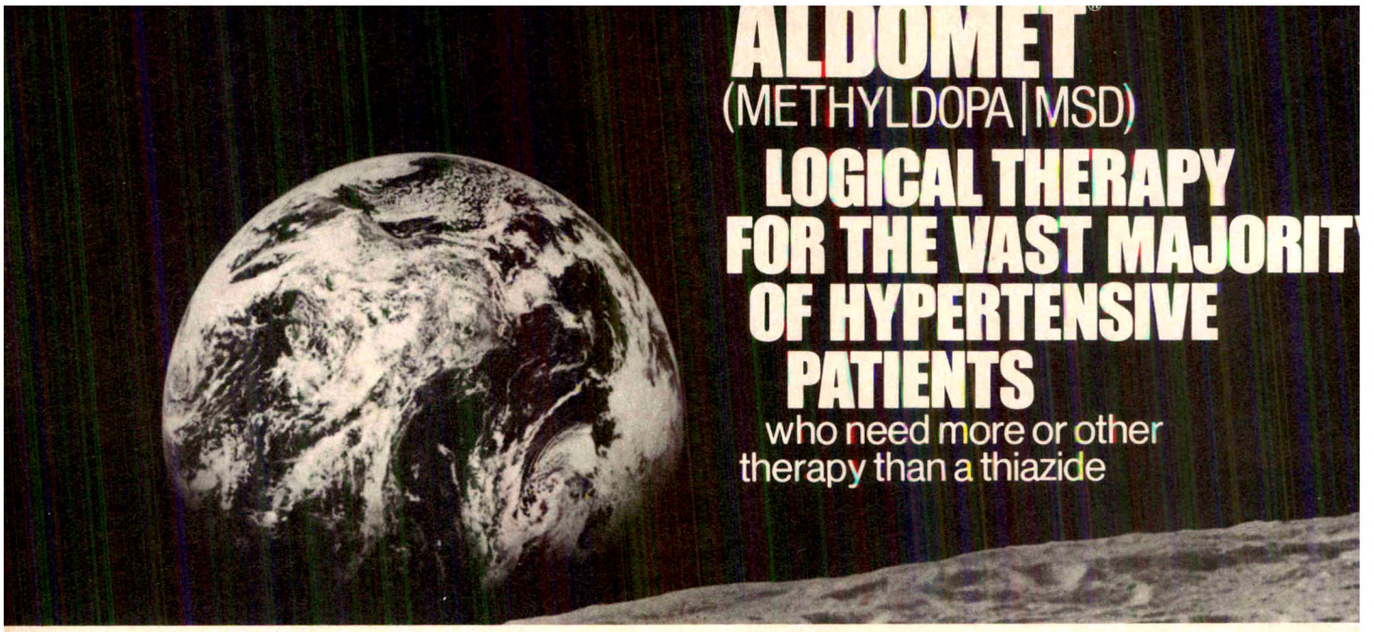
ALDOMET (Methyldopa, MSD) is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, please see the brief summary of prescribing information.



For a brief summary of prescribing information, please see following page.

MSD
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Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced
anesthetics; hypotension occurring durir
thesia usually can be controlled with vasop
Hypertension has recurred after dialysis in
on methyldopa because the drug is remove
procedure.

Adverse Reactions: *Central nervous syster*
tion, headache, asthenia or weakness, usu
and transient; dizziness, lightheadedness
toms of cerebrovascular insufficiency, pare
parkinsonism, Bell's palsy, decreased ment
involuntary choreoathetotic movements;
disturbances, including nightmares and r
mild psychoses or depression.
Cardiovascular: Bradycardia, aggravation
pectoris. Orthostatic hypotension (decrea
dosage). Edema (and weight gain) usually re
use of a diuretic. (Discontinue methyldopa
progresses or signs of heart failure appear.
Gastrointestinal: Nausea, vomiting, distenti
stipation, flatus, diarrhea, mild dryness o
sore or "black" tongue, pancreatitis, sialad
Hepatic: Abnormal liver function tests, j
liver disorders.
Hematologic: Positive Coombs test, hemol
mia. Leukopenia, granulocytopenia, thron
penia. Positive tests for antinuclear antib
cells, and rheumatoid factor.
Allergic: Drug-related fever, lupus-like sy
myocarditis.
Other: Nasal stuffiness, rise in BUN, breast
ment, gynecomastia, lactation, impoter
creased libido, dermatologic reactions i
eczema and lichenoid eruptions, mild ar
myalgia.

Note: Initial adult dosage should be lir
500 mg daily when given with antihyper
other than thiazides. Tolerance may occur
between second and third months of
increased dosage or adding a diuretic fr
restores effective control. Patients with
renal function may respond to smaller
Syncope in older patients may be related to ir
sensitivity and advanced arteriosclerotic
disease; this may be avoided by lower dose

How Supplied: Tablets, containing 125 mg
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250 mg methyldopa each, in single-unit pac
100 and bottles of 100 and 1000; Tablets, co
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For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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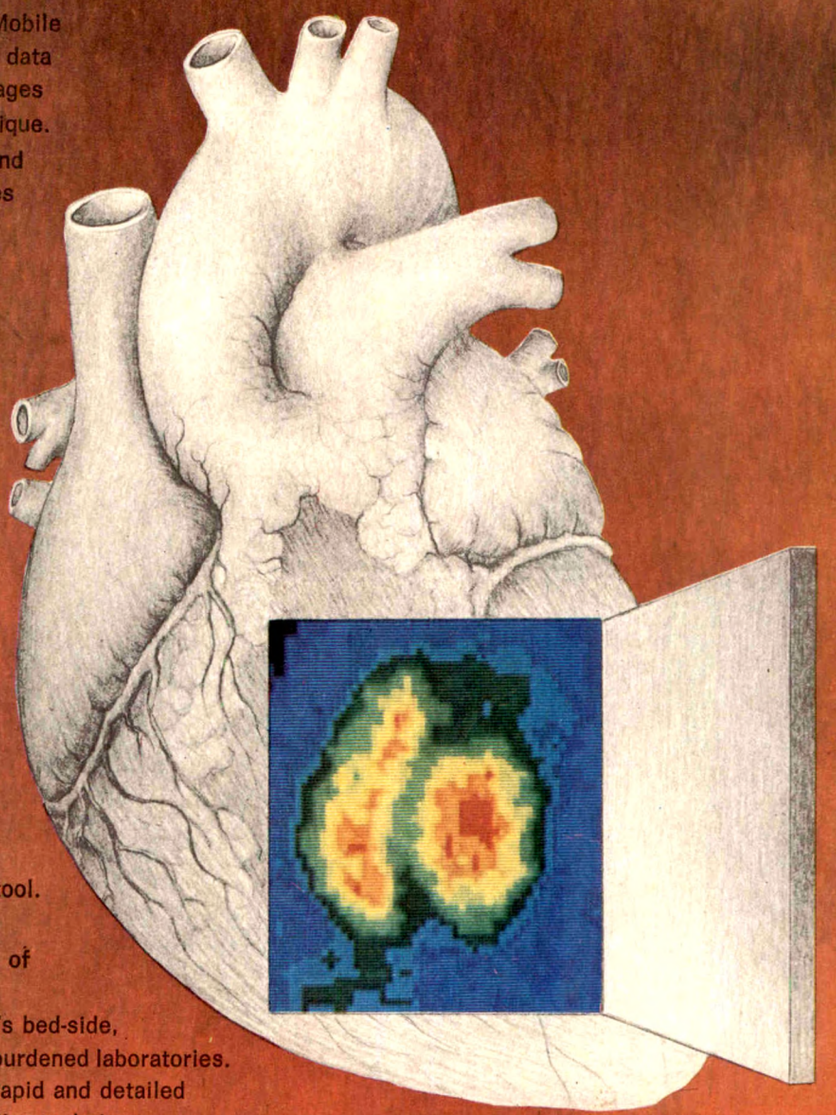
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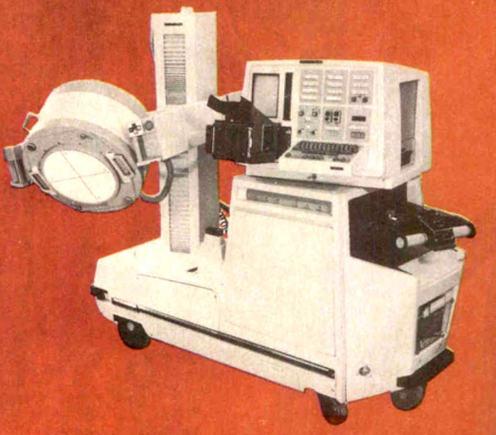
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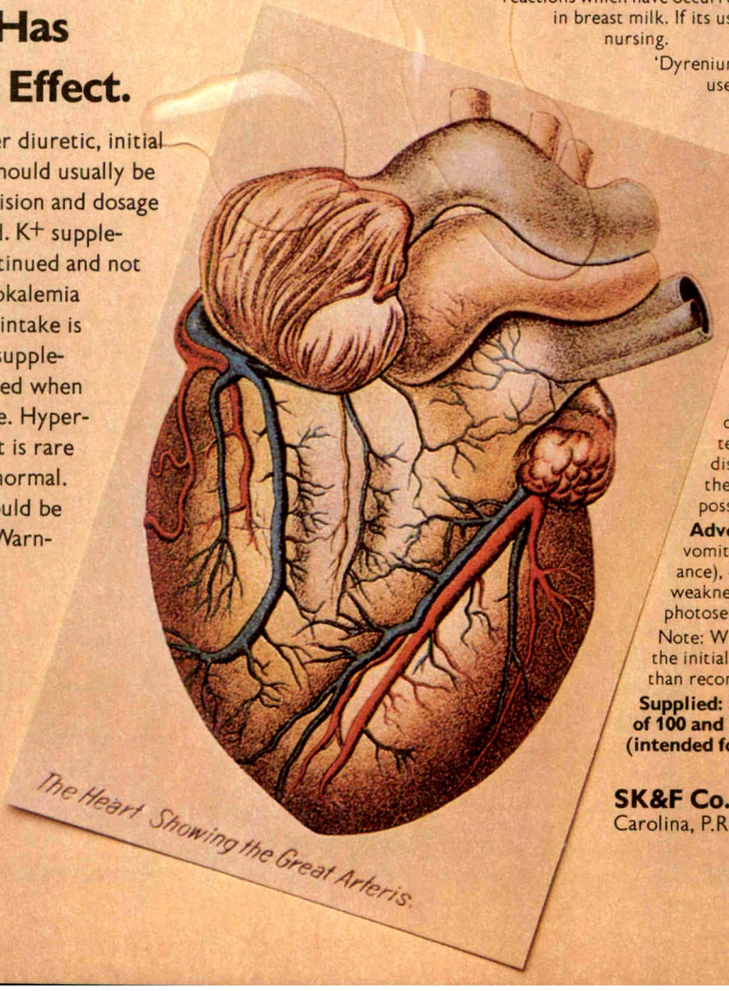
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1. Donaldson, E.K., et al.: *Brit. M.J.* 1:1254-5 (May 22) 1976.



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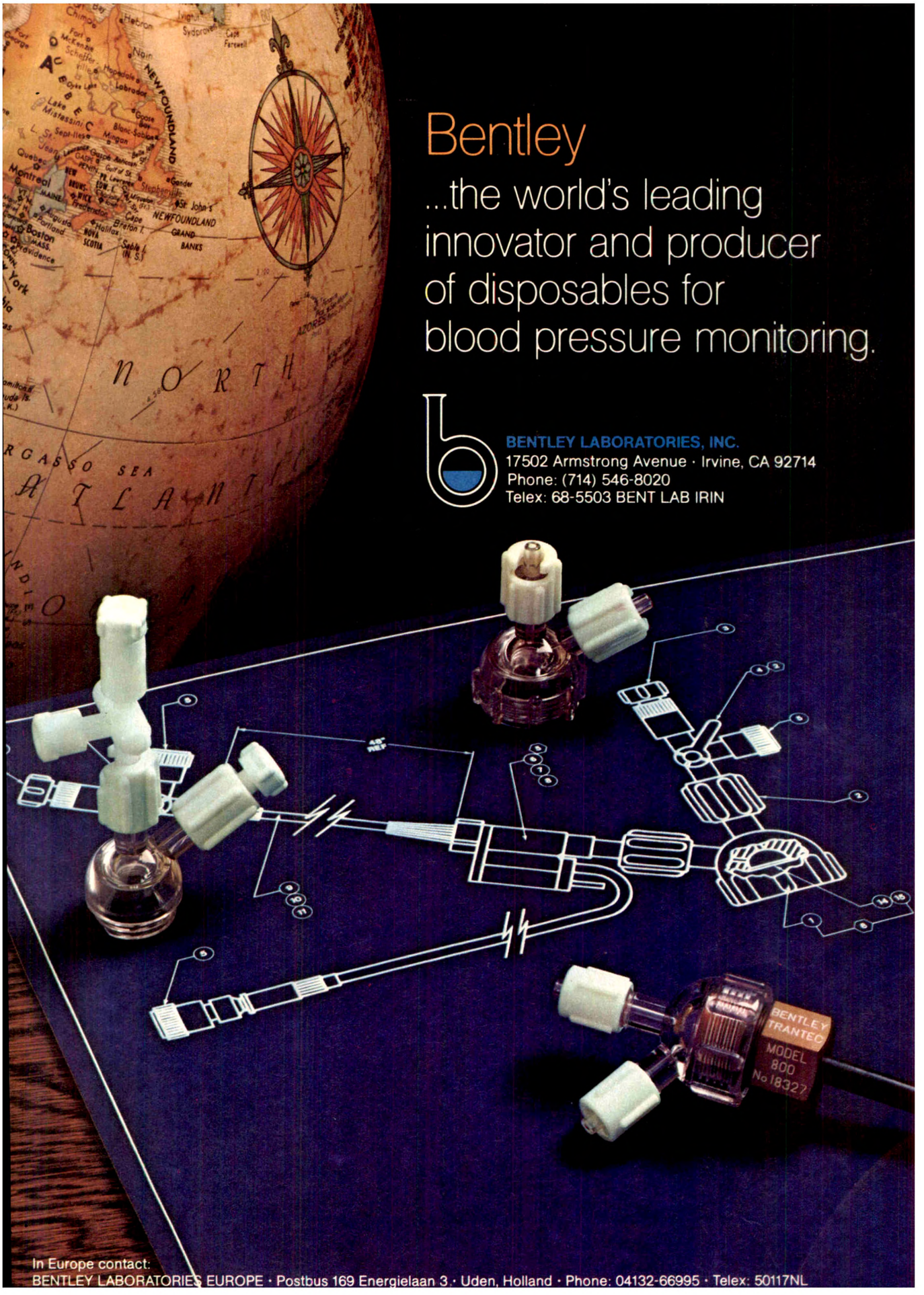
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Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

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DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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RONALD M. WEINTRAUB, JULIAN M. AROESTY, SVEN PAULIN, FREDERICK H. LEVINE, JOHN E. MARKIS, PAUL J. LaRAIA, STAFFORD I. COHEN and GEORGE F. KURLAND

The experience of these investigators over the past 7 years with patients having unstable angina indicates that institution of early and vigorous medical therapy rarely results in major infarction or death. In 60 patients unresponsive to an optimal medical program including administration of propranolol and nitrates, the institution of intraaortic balloon counterpulsation, cardiac catheterization and cardiac surgery yielded good results. One operative and one late death occurred in this group. Survivors followed up for 3 to 63 months have done well; 77 percent are considered employable and more than 90 percent are in functional class I or II. These data suggest that with the use of the intraaortic balloon pump, patients with unstable angina pectoris unresponsive to optimal medical treatment can be operated on with a mortality rate approaching that for chronic stable angina (less than 2 percent).

883 Medically Refractory Unstable Angina Pectoris. II. Hemodynamic and Angiographic Effects of Intraaortic Balloon Counterpulsation

JULIAN M. AROESTY, RONALD M. WEINTRAUB, SVEN PAULIN and PATRICK O'GRADY

Intraaortic balloon counterpulsation in 10 patients with angina pectoris refractory to maximal medical therapy significantly decreased systolic and end-diastolic left ventricular pressures with little effect on the cardiac index or left ventricular volume. Although left ventricular contractility appeared to be improved with use of the balloon, ventricular volumes and ejection fraction were not significantly altered. Discontinuation of counterpulsation resulted in increased left ventricular end-diastolic pressure and pulmonary arterial systolic and mean pressures without any significant change in heart rate or cardiac index. The symptomatic improvement after counterpulsation in these patients occurs mainly through the reduction in preload and afterload.

889 Prognostic Value of a Persistently Positive Technetium-99m Stannous Pyrophosphate Myocardial Scintigram After Myocardial Infarction

HAROLD G. OLSON, KENNETH P. LYONS, WILBERT S. ARONOW, JOHN KUPERUS, JOAN ORLANDO and DAVID HUGHES

A persistently positive myocardial scan was found in 54 percent of 138 patients in clinically stable condition 6 to 260 weeks after an acute myocardial infarction. Occurring more often in symptomatic rather than asymptomatic patients, a persistently positive myocardial scan proved to be the best single predictor of cardiac death and significantly augmented the predictive value of other clinical variables, including age, location of acute myocardial infarction, clinical status, electrocardiographic findings and chest X-ray findings. During a follow-up period of 11.6 + 6.9 months after scintigraphy, 42 percent of the patients with a persistently positive scintigram had either a cardiac death, a nonfatal myocardial infarction, unstable angina pectoris or congestive heart failure compared with 13 percent of patients with a negative scintigram.

Continued on page A13

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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

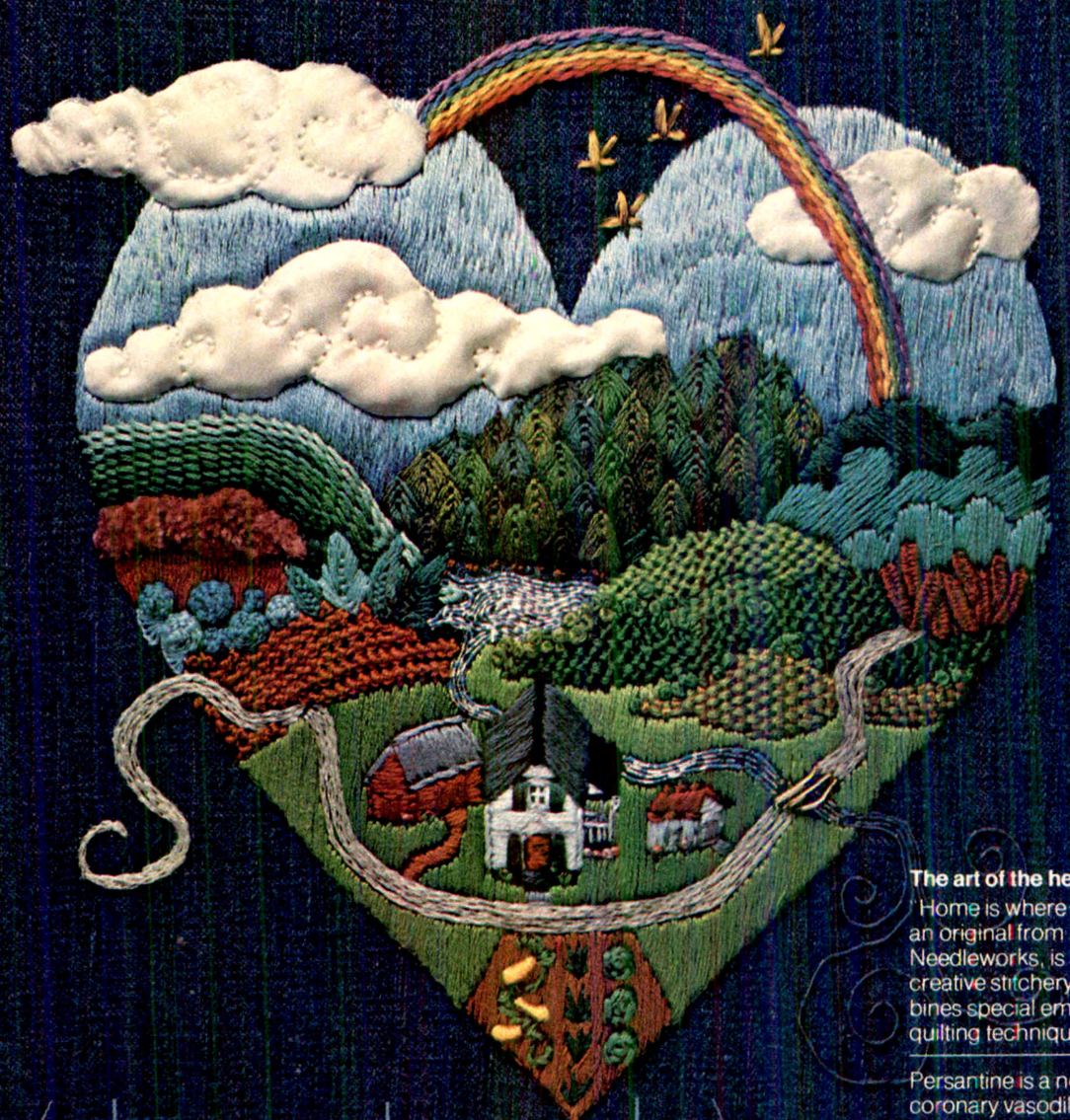
DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

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Persantine

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899 Single Dose Myocardial Perfusion Imaging With Thallium-201: Application in Patients With Nondiagnostic Electrocardiographic Stress Tests

DAVID M. McCARTHY, DAVID K. BLOOD, ROBERT R. SCIACCA and PAUL J. CANNON

In 128 patients undergoing diagnostic coronary arteriography, myocardial perfusion imaging with single dose exercise thallium-201 scans was significantly more sensitive (85 versus 64 percent) and more accurate (84 versus 71 percent) than stress electrocardiography in detecting coronary disease but offered no advantage in patients with diagnostically adequate stress electrocardiograms. None of the 22 patients with coronary artery disease and an inadequate stress electrocardiogram had an ischemic electrocardiographic response, although angina developed in 16 and 18 had a perfusion defect on scanning. These data suggest that the mechanisms producing ischemic S-T segment depression in the exercise electrocardiogram are not identical with those producing angina or an exercise scan defect.

907 Comparison of Treadmill Exercise Testing and Psychologic Stress Testing Soon After Myocardial Infarction

ROBERT F. DeBUSK, CRAIG BARR TAYLOR and W. STEWART AGRAS

In 20 men with coronary artery disease standard methods of physical exercise testing were superior to currently available psychologic stress tests for evaluating the cardiovascular response to most commonly encountered psychologic stressors. Cardiovascular values recorded during psychologic stress were substantially lower than those noted during treadmill exercise testing. Heart rate and systolic blood pressure responses at the onset of ischemic S-T segment depression were substantially greater during treadmill exercise than during psychologic stress testing. Although a physical stress does not simulate psychologic stress, it appears to provide a useful measure of the cardiovascular response that would be elicited by most but not all physical and psychologic stressors.

913 Right Ventricular Apical Activation Times in Patients With Conduction Disturbances Occurring During Acute Transmural Myocardial Infarction

ALVARO MAYORGA-CORTES, JOHN J. ROZANSKI, RUEY J. SUNG, AGUSTIN CASTELLANOS and ROBERT J. MYERBURG

His bundle and right ventricular apical (RVA) electrograms recorded in 18 patients with acute transmural myocardial infarction showed that the infarction in itself did not increase the duration of the V-RVA interval even when complete left bundle branch block was present. A prolonged V-RVA interval coexisting with a "complete" right bundle branch block pattern was not due to distal right bundle branch block but to a conduction disturbance located in the proximal portions of the right bundle or within the His bundle itself. This study extends the usefulness of the newer techniques of obtaining intracardiac electrograms to assess conduction defects and shows that the V-RVA interval can help categorize patients with an inferoposterior myocardial infarction, prolonged intraventricular conduction time and predominantly positive QRS deflections in scalar leads V_1 and V_2.

920 Regional Myocardial Function at Rest and After Rapid Ventricular Pacing in Patients After Myocardial Revascularization by Coronary Bypass Graft or by Collateral Vessels

MICHAEL SESTO and FRANZ SCHWARZ

This study of 194 patients with proximal disease of the left anterior descending coronary artery demonstrates that successful surgical revascularization preserves myocardial function as compared with "pure" coronary stenosis both during stress and at rest. A critical obstruction should be corrected with bypass grafting because cardiac function improves thereafter. When coronary stenosis progresses to occlusion without revascularization, myocardial contractility becomes depressed at rest and after pacing. Revascularization by collateral vessels preserves resting function in coronary occlusion to some extent but is ineffective after pacing. Successful surgical revascularization prevents loss of function at rest and after pacing in critical coronary stenosis and occlusion.

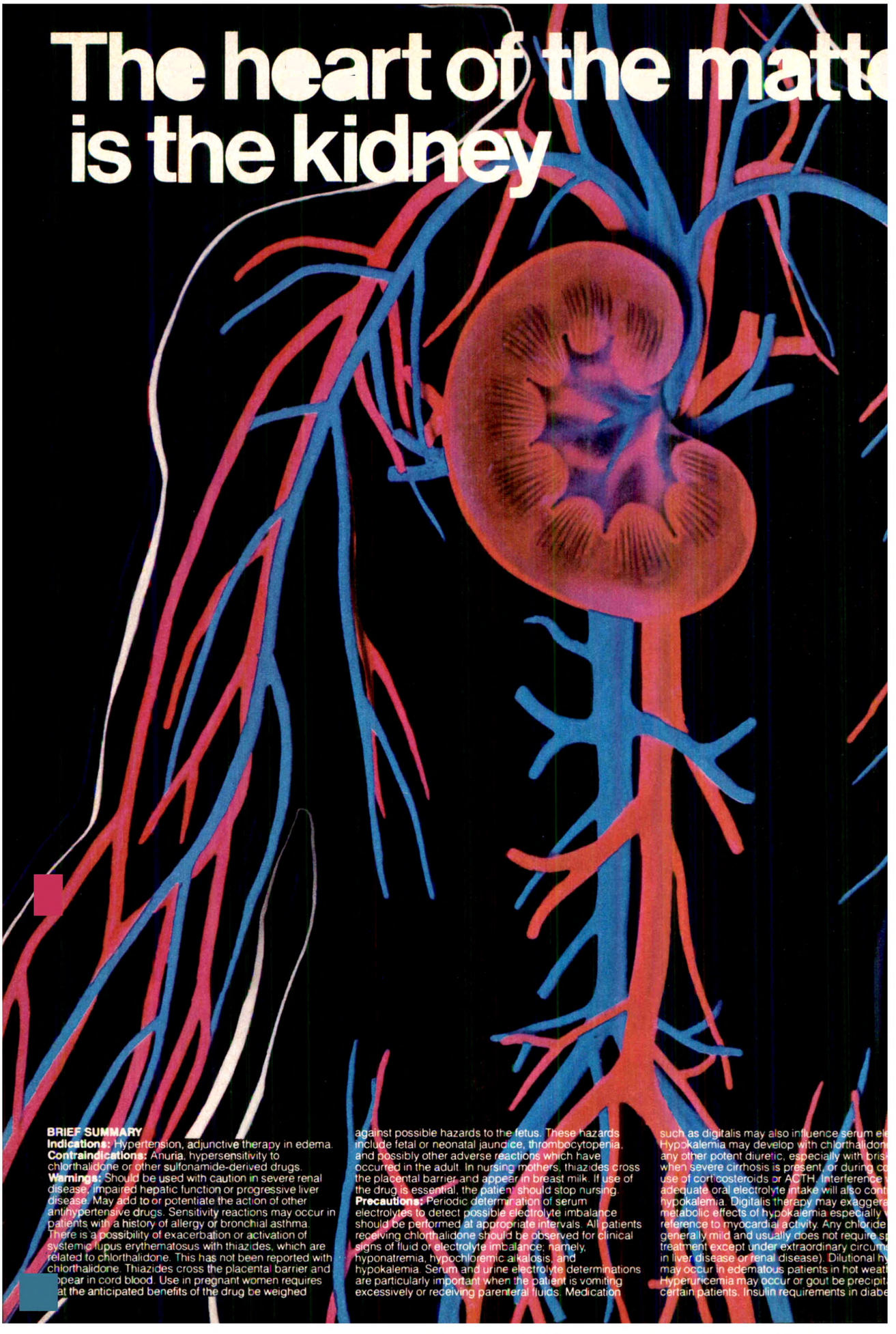
929 Influence of Preoperative Left Ventricular Function on Results of Homograft Replacement of the Aortic Valve for Aortic Stenosis

RICHARD THOMPSON, MAGDI YACOUB, MOHAMMED AHMED, RICARDO SEABRA-GOMES, ANTHONY RICKARDS and MALCOLM TOWERS

Although changes in ejection fraction have been widely used to assess left ventricular function after cardiac surgery and as a prognostic guide in the surgical treatment of coronary and valvular heart disease, this study in 103

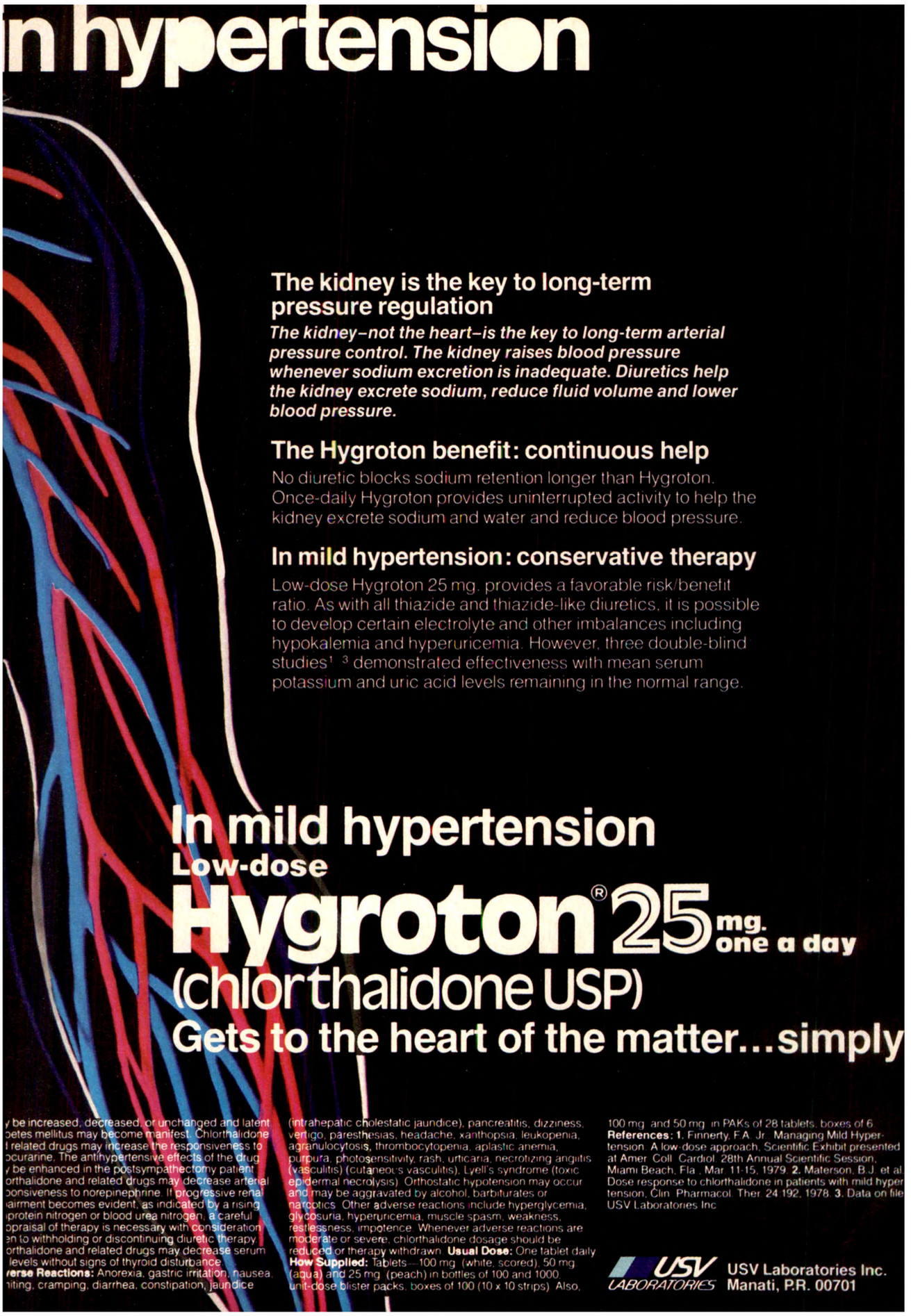
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The heart of the matt is the kidney



BRIEF SUMMARY
Indications: Hypertension, adjunctive therapy in edema.
Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.
Warnings: Should be used with caution in severe renal disease. Impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.
Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum el Hypokalemia may develop with chlorthalidon any other potent diuretic, especially with bris when severe cirrhosis is present, or during co use of corticosteroids or ACTH. Interference adequate oral electrolyte intake will also cont hypokalemia. Digitalis therapy may exagger metabolic effects of hypokalemia especially reference to myocardial activity. Any chloride generally mild and usually does not require s treatment except under extraordinary circum in liver disease or renal disease). Dilutional h may occur in edematous patients in hot weat Hyperuricemia may occur or gout be precipit certain patients. Insulin requirements in diabe

n hypertension



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y be increased, decreased, or unchanged and latent betes mellitus may become manifest. Chlorthalidone f related drugs may increase the responsiveness to ocurarine. The antihypertensive effects of the drug y be enhanced in the postsympathectomy patient orthalidone and related drugs may decrease arterial oonsiveness to norepinephrine. If progressive renal airment becomes evident, as indicated by a rising protein nitrogen or blood urea nitrogen, a careful opraisal of therapy is necessary with consideration en to withholding or discontinuing diuretic therapy. orthalidone and related drugs may decrease serum levels without signs of thyroid disturbance. **verse Reactions:** Anorexia, gastric irritation, nausea, niting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) and 25 mg. (peach) in bottles of 100 and 1000, unit-dose blister packs, boxes of 100 (10 x 10 strips). Also, 100 mg. and 50 mg. in PAKs of 28 tablets, boxes of 6.

References: 1. Finnerty, F.A. Jr.: Managing Mild Hypertension. A low-dose approach, Scientific Exhibit presented at Amer. Coll. Cardiol. 28th Annual Scientific Session, Miami Beach, Fla., Mar. 11-15, 1979. **2.** Materson, B.J. et al.: Dose response to chlorthalidone in patients with mild hypertension, Clin. Pharmacol. Ther. 24:192, 1978. **3.** Data on file, USV Laboratories Inc.

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SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe response can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

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patients with aortic stenosis concludes that poor left ventricular function does not increase the risk of aortic valve replacement for aortic stenosis and that improved left ventricular function can be expected in the majority of patients, including those with an ejection fraction of 0.45 or less. Impaired left ventricular function was associated with superimposed coronary artery disease. For this reason the authors recommend homograft valve replacement and, when necessary, additional coronary bypass grafting in patients with poor left ventricular function.

939 Use of Apexcardiography To Evaluate Left Ventricular Diastolic Compliance in Human Beings

JAN MANOLAS, HANS PETER KRAYENBUEHL and WILHELM RUTISHAUSER

The most important finding in this study of the relative amplitude measurements of the left apexcardiogram and internally derived indexes of diastolic compliance of the left ventricle was the close inverse correlation of the *A* wave amplitude/total diastolic deflection (A/D) ratio with specific compliance ($r = -0.8$). All patients with values over 44 percent for the A/D ratio had congestive cardiomyopathy. The A/D ratio separated these patients from those without left ventricular disease. The ratio of *A* wave height to total vertical deflection (A/H ratio) showed a highly significant correlation with left ventricular end-diastolic compliance ($r = -0.64$) and significantly lower correlations with end-diastolic distensibility index as well as specific compliance. Both ratios are useful noninvasive measurements of diastolic compliance of the left ventricle, but their validity for assessing such changes in the same subject or the presence of aortic or mitral valve disease or coronary artery disease requires further investigation.

946 Lack of Correlation Between Echocardiographic Pulmonary Valve Morphology and Simultaneous Pulmonary Arterial Pressure.

HARRY ACQUATELLA, NELSON B. SCHILLER, D. NORMAN SHARPE and KANU CHATTERJEE

Technically satisfactory pulmonary valve echograms in 16 of 29 patients showed no significant correlation between hemodynamic measurements and the echographic pulmonary valve *a* wave amplitude, diastolic E-F slope or the systolic opening B-C slope. The combination of mid systolic pulmonary valve notching and an absent *a* wave observed in more advanced degrees of pulmonary hypertension was specific but not sensitive for that condition. One cannot rely on echocardiographic features of the pulmonary valve in assessing the severity of pulmonary hypertension. They serve only as a rough guide to the presence of the more severe levels of pulmonary hypertension.

PEDIATRIC CARDIOLOGY

951 Maximal Exercise Stress Testing in Evaluation of Arrhythmias in Children: Results and Reproducibility

JOHN J. ROZANSKI, IVAN DIMICH, LEONARD STEINFELD and JOEL KUPERSMITH

Data obtained from two maximal treadmill exercise tests performed an average of 3.1 months apart in 19 children aged 15 to 16 years with chronic idiopathic ventricular and supraventricular arrhythmias confirm the usefulness and reproducibility of such testing to evaluate arrhythmias in children. All but one child achieved the expected maximal heart rate. No statistically significant difference was noted between the first and second exercise test in any child with regard to maximal heart rate and duration of maximal exertion. For ventricular arrhythmias maximal exercise testing yielded reproducible results in either suppressing or reducing the arrhythmias during both exercise periods. These results suggest that such exercise testing would be valuable in deciding to restrict or allow exertional activities and in monitoring the efficiency of antiarrhythmic drugs in children.

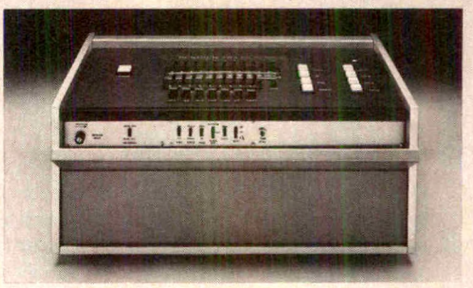
957 Echocardiographic Assessment of Discrete Subaortic Stenosis in Childhood

TERESA E. BERRY, KALIM U. AZIZ and MILTON H. PAUL

Echocardiographic and cardiac catheterization data in 17 young patients with discrete subaortic stenosis show that the end-diastolic h/r ratio (ratio of mean left ventricular septal and posterior wall thickness to one-half minor left ventricular cavity dimension) is a useful predictor of peak left ventricular pressure and that the LVOT/Ao (left ventricular outflow tract/aortic dimension) ratio is significantly reduced relative to that of control subjects. The LVOT/Ao ratio was helpful in differentiating patients with mild stenosis from those with more severe stenosis. Previously described echocardiographic abnormalities of the aortic valve such as flutter or early systolic closure could not be correlated with any specific type or severity of subaortic stenosis.

Continued on page A19

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CONTENTS

962 Unusual Vascular Anomalies Causing Persistent Pulmonary Hypertension in a Newborn

JEFFREY D. GOLDSTEIN, MARLENE RABINOVITCH, RICHARD VAN PRAAGH and LYNNE REID

This fatal case of an infant with a unique configuration of congenital pulmonary vascular anomalies and severe secondary changes of pulmonary arterial hypertension shows that (1) bronchopulmonary development may be relatively normal in spite of an aberrant pulmonary vascular supply, and (2) the unusual arterial anomalies represent an aberration in the normal embryologic sequence of pulmonary arterial development. Both the anatomic and histologic appearance of the anomalous arteries favor their origin from persistent primitive systemic arteries.

METHODS

969 Peak Left Ventricular Systolic Pressure/End-Systolic Volume Ratio: A Sensitive Detector of Left Ventricular Disease

THASANA NIVATPUMIN, STANLEY KATZ and JAMES SCHEUER

Seeking to evaluate peak pressure/systolic volume ratio as a detector of cardiac disease in 115 subjects undergoing diagnostic catheterization, these investigators found this ratio separated those with a diseased heart from those with a normal heart in those subjects with a normal ejection fraction (more than 60 percent). Those with a diseased heart had a greater end-systolic volume than normal subjects. The peak pressure/systolic volume ratio appears to be more sensitive than the ejection fraction in detecting subtle changes in myocardial function in patients other than those with pure aortic stenosis.

975 Monitoring Ventricular Function at Rest and During Exercise With a Nonimaging Nuclear Detector

HENRY N. WAGNER, Jr., PIERRE RIGO, RONALD H. BAXTER, PHILIP O. ALDERSON, KENNETH H. DOUGLASS and DANIEL F. HOUSHOLDER

Testing of this improved version of the nuclear stethoscope, a portable nonimaging device that measures beat to beat ventricular time-activity curves, showed that the correlation coefficient of left ventricular ejection fraction obtained with the device and with a camera-computer system was 0.92 in 35 subjects. During bicycle exercise the ejection fraction in 15 normal persons increased from 44 to 64 percent; among 12 patients with heart disease it was unchanged in 5 and decreased in 7. The mean peak exercise heart rates in the two groups were not significantly different. The improved performance of the current device occurs largely because one can properly position the detector when viewing the beat to beat time-activity curve that measures and displays the activity every 50 msec.

980 Method for the Rapid and Atraumatic Insertion of Permanent Endocardial Pacemaker Electrodes Through the Subclavian Vein

PHILIP O. LITTLEFORD, VICTOR PARSONNET and S. DAVID SPECTOR

Using a specially constructed peel-away introducer, 17 different physicians successfully implanted 164 permanent pacemakers through the subclavian vein. Fourteen attempts (8.5 percent) were unsuccessful. This procedure is rapid and atraumatic and requires no surgical dissection.

REPORTS ON THERAPY

983 Effects of Digoxin on Sinus Nodal Function Before and After Vagal Blockade in Patients With Sinus Nodal Dysfunction

JAMES A. REIFFEL, J. THOMAS BIGGER, Jr. and MARVIN CRAMER

Studying the effects of intravenously administered digoxin on sinus nodal function in 34 patients with sinus nodal dysfunction, these investigators found that this drug may have direct excitatory, adrenergic or previously unrecognized vagolytic effects on sinus nodal function in man and their manifestation may depend on heart rate or autonomic tone. These data suggest that most patients with sinus bradycardia or sick sinus syndrome can be given digitalis safely for the therapy of cardiac arrhythmias or ventricular failure. When the safety of digoxin administration in a patient with sinus nodal dysfunction is in question and other therapeutic interventions such as pacemaker insertion depend solely on the effects of its administration, acute digitalization during electrophysiologic testing of sinus nodal function may quickly and safely suggest the results to be expected during long-term administration.

Continued on page A21

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CONTENTS

990 Combined Therapy With Digoxin and Nitroprusside in Heart Failure Complicating Acute Myocardial Infarction

DANIEL S. RAABE, Jr.

In 11 patients with congestive heart failure complicating acute myocardial infarction the intravenous infusion of nitroprusside significantly decreased the pulmonary arterial wedge pressure, mean arterial pressure and systemic vascular resistance and increased the cardiac index. The addition of digoxin administered intravenously further increased cardiac output but did not further decrease pulmonary arterial wedge pressure. The improved cardiac output after digitalis is attributed to the positive inotropic effect of this drug or decreased myocardial ischemia with a resultant improvement in the contractile characteristics of the ischemic zone. These results suggest the usefulness of this combination of a positive inotropic agent and a vasodilator in the treatment of congestive heart failure complicating acute myocardial infarction.

995 Lack of Ouabain Effect on Pacing-Induced Myocardial Ischemia in Patients With Coronary Artery Disease

HENRY S. LOEB, NANCY STREITMATTER, DAVID BRAUNSTEIN, WILLIAM R. JACOBS, ROBERT P. CROKE and ROLF M. GUNNAR

Studying the acute effects of digitalis in 16 patients with angiographically proved two and three vessel coronary artery disease and no clinical heart failure, these investigators found that the nine patients with a normal ejection fraction responded differently to pacing than the seven patients with a reduced ejection fraction and that ouabain administration did not significantly alter the hemodynamic, metabolic or clinical response to pacing. These data do not support the routine use of digitalis in patients with coronary artery disease and a reduced ejection fraction. They do not contraindicate digitalis therapy for the control or prevention of supraventricular arrhythmias in patients with coronary artery disease but without clinical heart failure.

1001 Effects of Digitalis on Normal and Abnormal Left Ventricular Segmental Dynamics

JAY H. KLEIMAN, EDWIN L. ALDERMAN, ROBERT H. GOLDMAN, NEIL B. INGLES, GEORGE T. DAUGHTERS II and EDWARD B. STINSON. With the technical assistance of ANNE SCHWARZKOPF, CATHERINE KUSNICK and CAROL MEAD

Continuous ventricular dynamics were assessed in nine patients with stable coronary artery disease after the administration of 1 mg of intravenous digoxin. In patients with chronic left ventricular contraction abnormalities, deterioration of performance in abnormal regions after digoxin resulted from increased stress imposed by increased afterload and by improved segmental dynamics in more normal areas. The response of individual segments to digoxin depends on the amount of viable nonischemic muscle in the ventricular wall. In ventricles with prior scarring, administration of digoxin results in greater heterogeneity and asyneresis of myocardial segment performance due to further deterioration of function in some segments, although global left ventricular function is improved.

1009 Effect of Isosorbide Dinitrate on Response to Submaximal and Maximal Exercise in Patients With Congestive Heart Failure

JOSEPH A. FRANCIOSA and JAY N. COHN

Hemodynamic and clinical data in 18 patients with class II to IV congestive heart failure demonstrated that the short-term administration of isosorbide dinitrate did not improve maximal exercise capacity or left ventricular performance at maximal exercise but did improve pump function at submaximal work loads and enabled the patients to perform limited exercise more comfortably. After administration of this drug the resting pulmonary wedge pressure and systemic vascular resistance were significantly reduced, but the exercise duration was not altered and maximal oxygen consumption was not significantly changed.

REVIEW

1015 Strategy for Evaluation and Surgical Treatment of the Asymptomatic or Mildly Symptomatic Patient With Coronary Artery Disease

STEPHEN E. EPSTEIN, KENNETH M. KENT, ROBERT E. GOLDSTEIN, JEFFREY S. BORER and DOUGLAS R. ROSING

Although incomplete data prevent the synthesis of a consistent and scientifically defensible strategy for the evaluation and treatment of all patients with coronary artery disease, the following practical strategy seems reason-

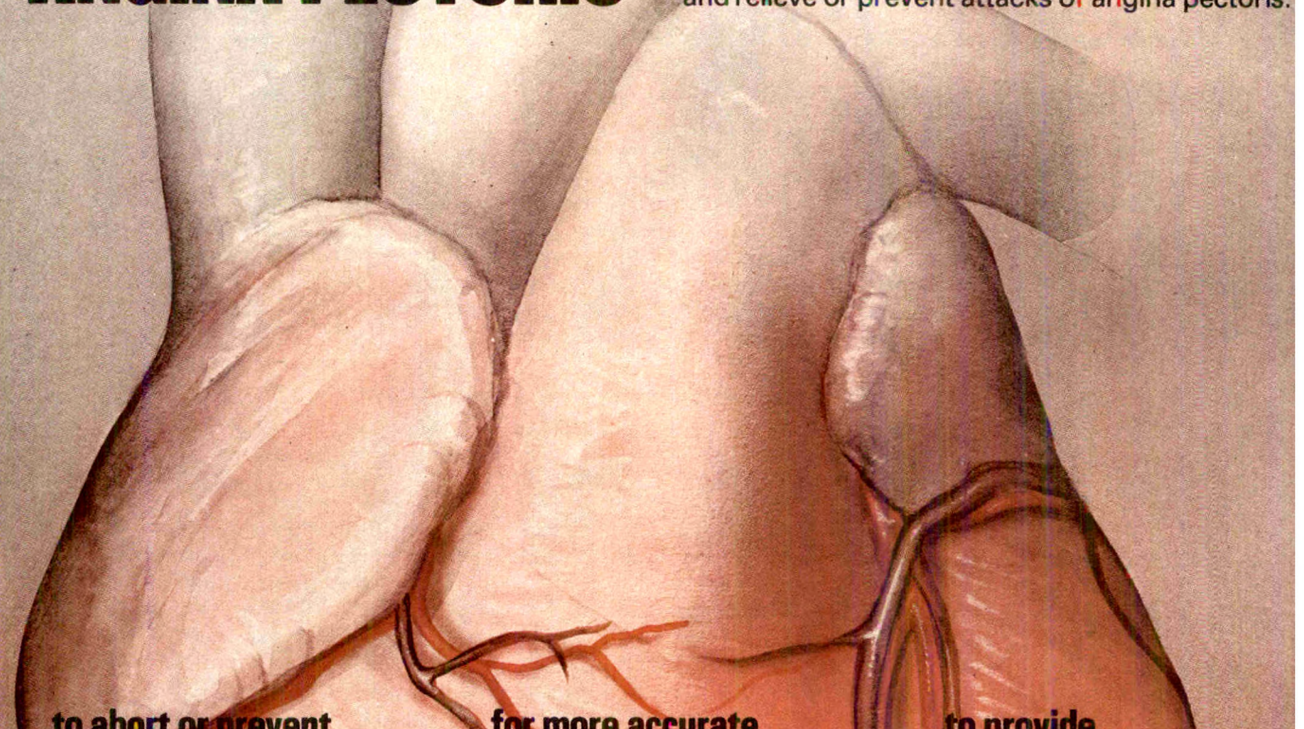
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"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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able: The patient with a life style restricted by angina despite medical therapy is a candidate for cardiac surgery and possible coronary bypass surgery, particularly when significant narrowing of the left main coronary artery is present. Those who have mild symptoms of coronary artery disease or have had a previous myocardial infarction merit coronary and left ventricular cineangiography, and operation should be performed in those with significant disease of the left main coronary artery. It is medically and economically impractical to screen asymptomatic patients for coronary artery disease. Cardiac catheterization should not be routinely performed in asymptomatic patients with positive exercise tests. For these patients risk factors, if present, should be rigorously treated.

HISTORICAL MILESTONES

1026 Historical Development of Concept of Blood Circulation: An Anniversary Memorial Essay to William Harvey

JACK D. KEY, THOMAS E. KEYS and JOHN A. CALLAHAN

This refreshing journey down the arterials of cardiovascular history pays tribute to William Harvey and his modern concept of the circulation of the blood. Despite its emphasis on the past, it must raise questions in the mind of the thoughtful cardiologist because similar delays in recognizing obvious cardiovascular conditions (for example, mitral valve prolapse) still abound. Santayana once observed that one who does not know the past is condemned to repeat it. Is the converse true? If we pay attention to the past, can we escape repeating it? This exciting scholarly essay provides some answers to this question.

DIAGNOSTIC SHELF

1033 Paroxysmal Nonreentrant Tachycardias Due to Simultaneous Conduction in Dual Atrioventricular Nodal Pathways

GEORGE CSAPO

Electrophysiologic studies in a 41 year old man confirmed that his multiple arrhythmias were due to dual atrioventricular (A-V) nodal pathways with simultaneous dual fast and slow conduction of single atrial beats at a normal basic sinus rate. A survey of reported studies indicates that dual A-V nodal pathways were documented in 17 (4.2 percent) of 405 patients studied. These observations strengthen the hypothesis that double conduction of a single atrial beat can play an important role in the genesis of some premature supraventricular beats and bigeminy and lead the investigator to postulate a hypothetical model of A-V nodal conduction.

1046 Systolic Click From a Swan-Ganz Catheter: Phonoechocardiographic Depiction of the Underlying Mechanism

JEFFREY M. ISNER, JACK HORTON and JAMES A. RONAN, Jr.

Insertion of a Swan-Ganz catheter in a 54 year old woman produced a loud mid systolic click indistinguishable from that considered classic for atrioventricular prolapse. The click apparently arose from the crisp slapping of the catheter against the ventricular septum. Echocardiograms indicated that the fortuitous combination of rapid posterior catheter motion and rapid anterior septal motion was the critical factor that allowed catheter-septum contact and the resultant systolic click. Removal of the catheter eliminated the click.

1049 Mid Systolic Notching of the Pulmonary Valve in the Absence of Pulmonary Hypertension

WILLIAM BAUMAN, L. SAMUEL WANN, RICHARD CHILDRESS, ARTHUR E. WEYMAN, HARVEY FEIGENBAUM and JAMES DILLON

Although normal right ventricular and pulmonary arterial pressures were simultaneously recorded, the pulmonary valve echogram in a 19 year old patient with idiopathic dilatation of the pulmonary artery showed a prominent mid systolic closing motion or notching indistinguishable from that seen in pulmonary hypertension. This case demonstrates that factors other than elevated pulmonary arterial pressure may be involved in producing mid systolic notching of the pulmonary valve.

CASE REPORTS

1053 Disopyramide-Induced Ventricular Fibrillation

W. JAY NICHOLSON, C. EDWIN MARTIN, JACK G. GRACEY and H. ROEBLING KNOCH

Recurrent ventricular fibrillation in three patients closely followed the institution of oral disopyramide therapy in only moderate doses. In each case the electrocardiogram showed a prolonged Q-T interval, normal QRS dura-

Continued on page A24

tion and episodes of ventricular fibrillation. After treatment with the drug was stopped, the subsequent electrocardiograms returned to normal and no more ventricular fibrillation occurred. These episodes of quinidine-like syncope were precipitated by disopyramide. Patients receiving disopyramide should be closely monitored for ventricular tachyarrhythmia and disproportionate repolarization changes and administration of the drug should be stopped if such changes are detected.

EDITORIAL

1056 Recent Advances in Digitalis Research
DEAN T. MASON and NAJAM A. AWAN

SPECIAL DEPARTMENTS

1060 Letters to the Editor

Interspersed Advertising—D. Indra, L. F. Le Jacq
More on Coronary Bypass Surgery—I, II, III, IV—H. Davies, D. H. Spodick, G. B. Prozan, G. F. O. Tyers, E. H. Williams
Retrograde Crossing of Aortic Bjork-Shiley Prosthesis—R. E. Falicov, W. F. Walsh, S. Wolfson
Significance of Chest Pain During Treadmill Exercise—J. M. Detry, M. F. Rousseau, J. P. Cole, M. H. Ellestad
Cardiopulmonary Resuscitation After Age 65—L. S. Baer

1066 American College of Cardiology News

CORRECTION

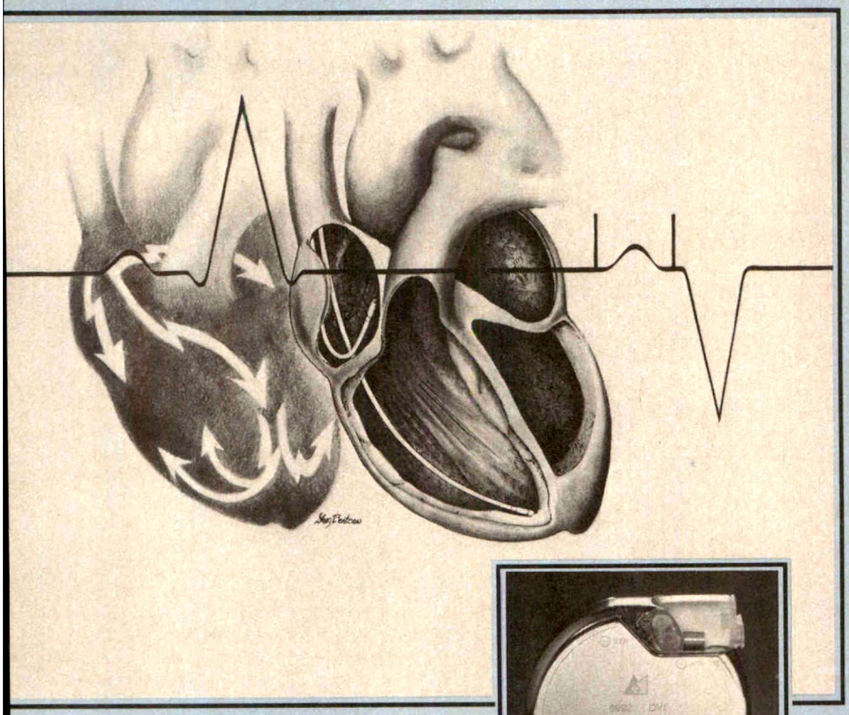
An error appeared in the abstract of "Effects of Intraaortic Balloon Counterpulsation on Regional Myocardial Function During Acute Coronary Occlusion in the Dog" by Sasayama S, Osakada G, Takahashi M, Hamashima H, Hirose K, Nishimura E and Kawai C (Am J Cardiol 43:59–66, 1979). The seventh sentence should read, "Balloon pumping produced no change in the dyskinetic motion of the ischemic segment or in compensatory augmentation of shortening of the control segment."



Pacing News

PHYSICIAN SERVICE OF MEDTRONIC, INCORPORATED VOL. 1, NO. 1

ledtronic Unfolds
IEW A-V SEQUENTIAL PACEMAKER





ltronic's new Byrel™ implantable pacemaker gned for A-V sequential pacing.

Both temporary and permanent A-V sequential pacing are likely to see more frequent applications because of two new products recently developed by Medtronic, Inc., Minneapolis, Minn. These products are the Byrel™ implantable A-V sequential pacemaker and the Model 5330 external A-V sequential pacemaker.

Interest in A-V pacing is growing because of this pacing mode's potential for both improving cardiac output and for control of certain tachyarrhythmias.

Restoration of A-V synchrony can improve cardiac output by providing regular atrial filling of the ventricles and by providing more normal valve function in some patients.

It may also prevent retrograde pumping by the atria and increase the efficiency of myocardial oxygen use (when compared to ventricular pacing).

A-V sequential pacing will also prevent most forms of retrograde atrial stimulation and bradycardia.

Controlled A-V synchrony provides a method for management of certain tachyarrhythmias preventing the long PR intervals necessary for some of the re-entry tachyarrhythmias. Of course, it can also prevent atrial bradycardia in brady-tachy syndrome and drug-induced bradycardia. A-V sequential pacing can also overdrive ventricular arrhythmias while providing the bene-

A-V SEQUENTIAL continued on page 2

rel® and Xyrel®-VP Pacemakers Earn 99.9% Performance Rating

edtronic's Xyrel® and Xyrel®-VP emakers are daily setting new relity records at Medtronic, earning a formance index of 99.9%. That ns that 99.9% of these products can xpected to perform within specificaover the next six-month period.

date, nearly 73,000 Xyrel® pacers have been sold in the U.S.—aculating in the past three years ly three-quarters of a million imt device months.

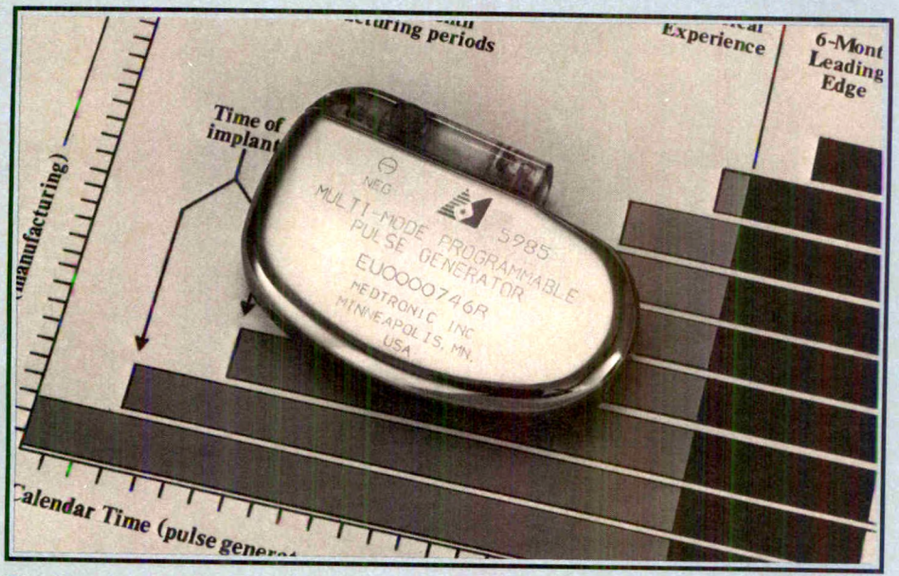
t, the number of units verified to be of specification when returned to Medtronic is extremely low—only 18 actual "out of spec" units have been observed by Medtronic technicians. Thus, the current performance index for both the Xyrel® and the Xyrel® -VP units is 99.9%.

The Medtronic Performance Index is a patient management tool developed by the company to provide up-to-date device performance information for the physician. Its unique value is that it is not diluted by early, historical product experience and it covers only presently implanted devices.

Of the total Xyrel® pacemakers sold, about 13,000 have consisted of Xyrel®-VP ventricular programmable units. Of these, only one has been observed to have a component failure by Medtronic technicians.

The performance index for each individual pacemaker is reported quarterly to the physician with Medtronic's Implant Data Report. Ask your Medtronic representative for a brochure giving details of the Medtronic Performance Index, or send in the coupon following Product Information Summary.

Spectrax™ Pacemaker in Clinical



The Spectrax™-SX multi-programmable pulse generator weighs only 45 grams and has a volume of 21 cc.

The new Spectrax™-SX multi-pro mable pacemaker is now under clinical evaluation. The first impla performed on a 44-year-old m Miami, Fla., in November, 1978. T vestigation has been expanded to centers across the country.

"Whenever a new pacing product is developed, it creates interest in the m community," says Spectrax™ marketin ager, Dennis Sellke. "But, Medtr Spectrax™ pacemaker, because of th ibility built into its programmable mod functions, has generated early and unu high excitement. The Spectrax™ pace represents significant and important te logical progress in pacing," Sellke say

Using the most modern micro-pr sor technology, the Spectrax™-SX maker will offer the physician atr ventricular asynchronous, atrial o tricular inhibited, and atrial or ven lar triggered modes. This pacema several programmable parameter clude pacing rate (30 to 150 beat minute), pulse width (.05 to 2.0 m amplitude, sensitivity, refractory hysteresis.

A-V SEQUENTIAL continued

fits of improved cardiac output.

Making these benefits available to the physician and his patient are Medtronic's A-V sequential pacing products. Leading off is the new Byrel™ a programmable, lithium-powered, ventricular-inhibited device with seven A-V programs and one ventricular-inhibited mode (atrial unit shut-down).

The Byrel™ has many of the performance features of other Medtronic pulse generators, including a lithium power source, titanium external covering, hermetically sealed hybrid electronics and more. Of course, both atrial and ventricular leads are required.

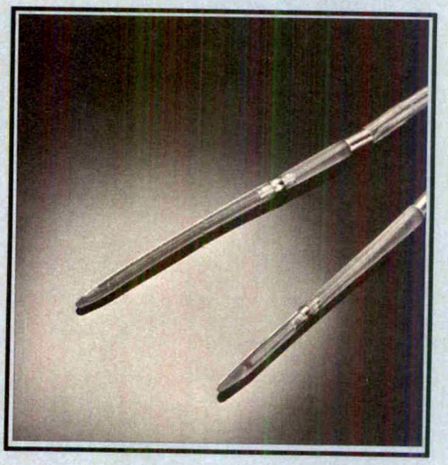
A companion to the Byrel™ is Medtronic's new 5330 external pacemaker designed for temporary atrial, ventricular or A-V sequential pacing.

In addition to its use in temporary pacing and diagnostic applications, you can also measure atrial or ventricular current stimulation thresholds with the 5330. It can also approximate R-Wave potentials sensed via ventricular pacing lead electrodes.

Amplitude of atrial and ventric output pulses is set separately by vidual controls. You can also ac ventricular sensitivity, ventricular and A-V interval.



Model 5330 external pacemaker for atrial, ventricular or A-V sequential pacing.



Implantable atrial pacing leads. The unit with the short electrode spacing (6992A) is designed for A-V sequential pacing.

LEADS

Atrial pacing requires leads desi to deal effectively with the insertio dislodgement problems of atrial p ment. Three J-shaped leads (Mo 6990 bipolar, 6991 unipolar and 69 polar) facilitate placement and s electrode placement in the right a appendage. Two coronary sinus bi endocardial leads (Models 6992 6992A) are designed for placeme the coronary sinus for permanent a pacing and sensing applications. electrode configuration of the 69 6990 and 6994 is specifically desig for enhancement of A-V sequential pa

Medtronic also provides a tempo disposable bipolar lead (Temptr Model 6705). It features a needle/i ducer designed for easier handling ing venous introduction. Its "push ton," detachable connector per complete removal of the percutane introducer cannula. This lead has b used for atrial pacing from the coro sinus and ventricular pacing from right ventricular apex.

Since A-V sequential pacing does depend on a functional A-V conduc system, there are no major contrainc tions to this mode of therapy.

Medtronic Helping you help the pacemaker patient

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MEDTRONIC® PRODUCT INFORMATION SUMMARY

Medtronic® External Pacing Products

Intended Use—The Model 5330 external pulse generator is intended for use with pacing lead systems for temporary cardiac pacing where such procedures are indicated for therapeutic, prophylactic or diagnostic purposes. The Model 5330 may be used for temporary atrial, ventricular or A-V sequential pacing.
Contraindications—Atrial pacing should be used only in patients with intact A-V conduction systems. The existence of anomalous conduction pathways bypassing normal A-V conduction is a potential contraindication for atrial stimulation. In the A-V sequential pacing mode, use of the Model 5330 with certain implanted lead systems may be contraindicated. See the 5330 technical manual for more information.
Warnings—All electrical equipment that is used invasively or attached to a pacing lead system increases the patient's chances of exposure to potentially hazardous leakage currents. For complete information on the quality and degree of such exposure, consult the technical literature supplied with each product.
Precautions—All man-made devices are subject to malfunction. Appropriate standby equipment should be immediately available when temporary pacing is employed.
Potential Complications—Major potential complications related to temporary pacing are asystole following abrupt cessation of pacing and lead-system-related problems. Atrial stimulation carries, in addition, the potential complication of accidental high-rate ventricular stimulation possibly resulting in ventricular tachycardia or fibrillation.

Medtronic® Implantable Pulse Generators

Intended Uses—Ventricular pacing using an implantable ventricular pulse generator and lead system are for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems. Cardiac pacing using an implantable A-V sequential pulse generator is for long-term therapeutic control of heart rate in patients where restoration of A-V synchrony is indicated to improve cardiac output or to protect against arrhythmias related to sequence of cardiac impulse propagation.
Contraindications—There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.
Warnings—Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.
Precautions—The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.
Side Effects—Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

Medtronic® Implantable Pacing Leads and Accessories

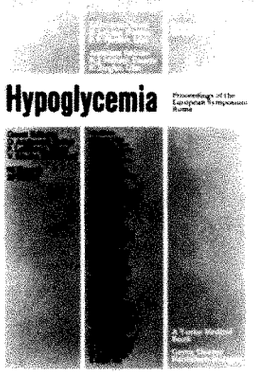
Intended Use—Medtronic® Implantable pacing leads are designed to be used with Medtronic® pulse generators as part of a cardiac pacing system (see product labeling for specific directions regarding applications).
Contraindications—Endocardial pacing leads are contraindicated in the presence of tricuspid valvular disease.
Warnings—An implanted lead or lead/adaptor combination constitutes a direct, low resistance current path to the myocardium. During the connection and testing procedures, only battery-powered pulse generators should be used with the lead system to protect against ventricular fibrillation induced by alternating current leakage. Extreme caution must be taken to properly ground all line-powered equipment used in the vicinity of the patient. Lead adaptors, lead extenders and repair kits should not be used if the integrity of the lead is in doubt.
Precautions—The pacing system may cease to function due to lead-related problems such as displacement, fracture, fibrotic tissue formation and elevated thresholds.
Side Effects—Body rejection phenomena, infection, erosion or migration through body tissue, transvenous lead-related thrombosis, embolism.
How Supplied—Medtronic® permanent implantable leads and accessories are supplied sterilized and, in most cases, individually packaged.

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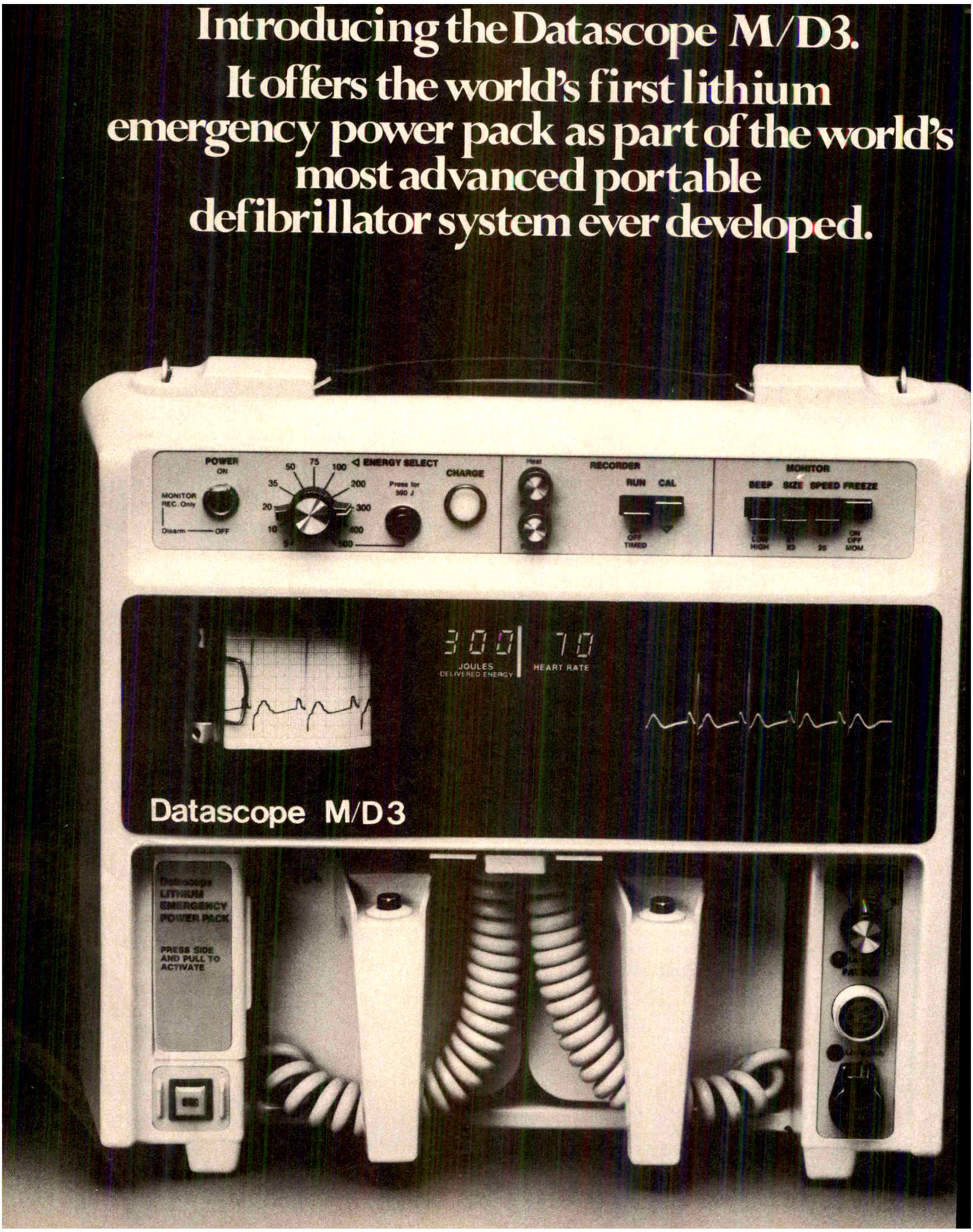
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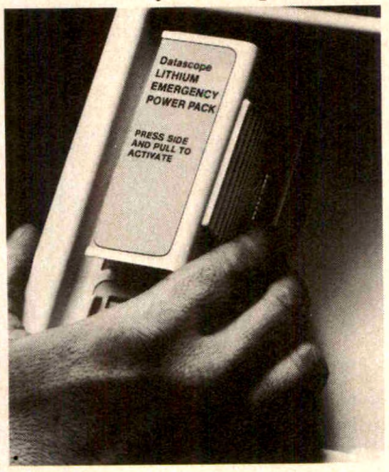
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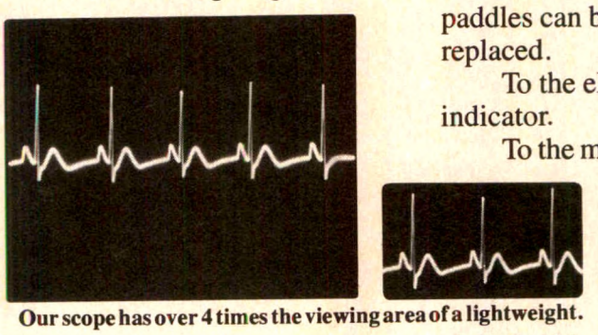
But unlike conventional systems, the M/D3 puts an end to the worry about battery failure. Because, in addition to having nickel cadmium batteries, the M/D3 also has a revolutionary back-up battery:



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Our scope has over 4 times the viewing area of a lightweight.

display of heart rate. And, naturally, it has the quality and performance you'd expect from the world's largest manufacturer of battery-powered monitors.

Despite its size, the M/D3 is available in a 500 joule as well as a 400 joule version. Either model incorporates a digital energy meter that precisely displays anticipated delivered energy.

Overall, the M/D3 offers those innovative details which create functional design elegance.

From the way all the operating controls are arranged in a single plane.

To the unique, dynamic calibration markers on the scope that give you an on-going indication of the sensitivity of



the trace.

To the document switch on the paddles which triggers the strip chart recorder. To the convenient way in which the paddles can be removed and replaced.

To the electrode lead fault indicator.

To the manner in which the battery pack can be rapidly ejected for replacement.

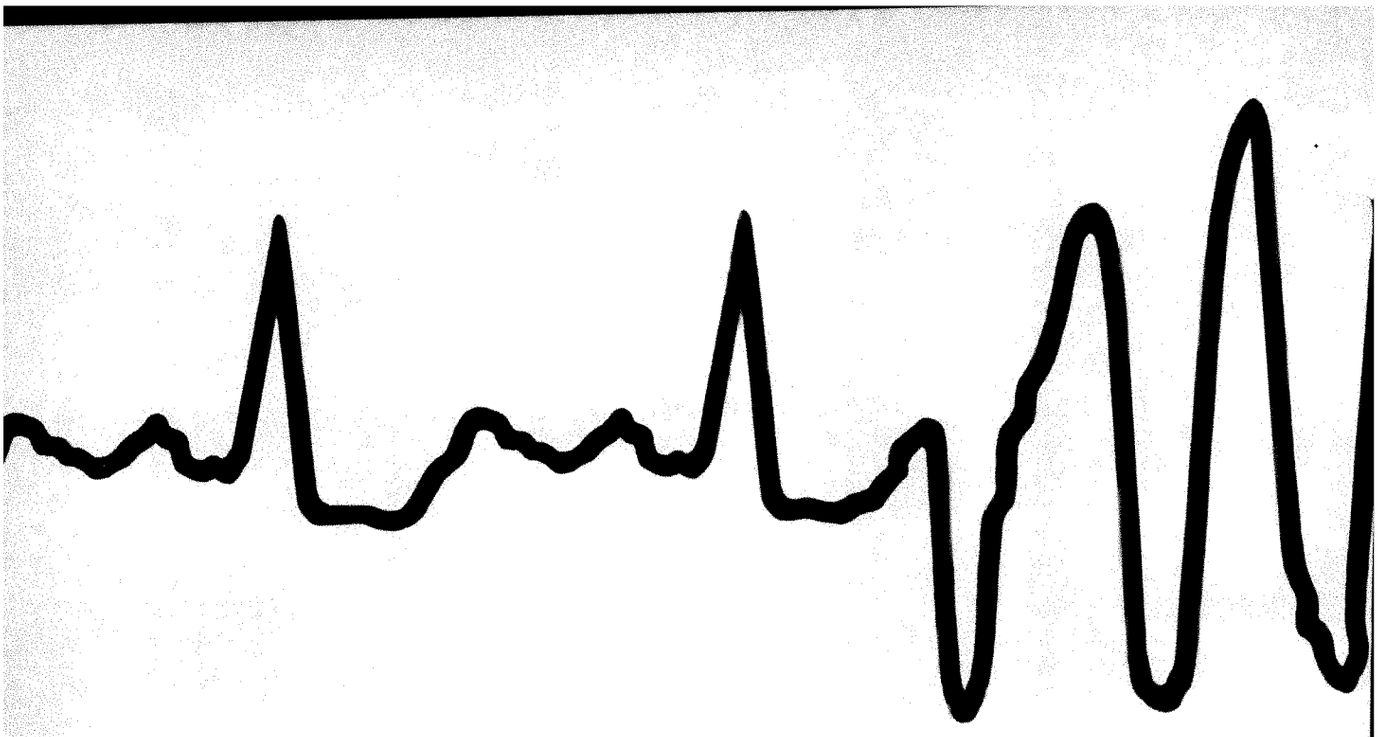
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Frankly, there are so many exciting features in the M/D3, there's simply not enough space to discuss them all here. We urge you to see the M/D3 first-hand. To arrange for a demonstration call us at 201-265-8800. Datascope Corp., Box 5-S , Paramus, NJ 07652.

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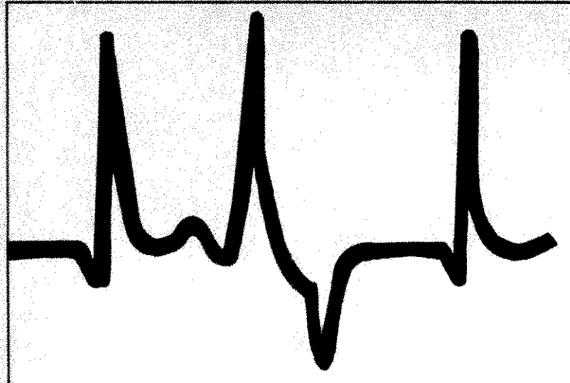
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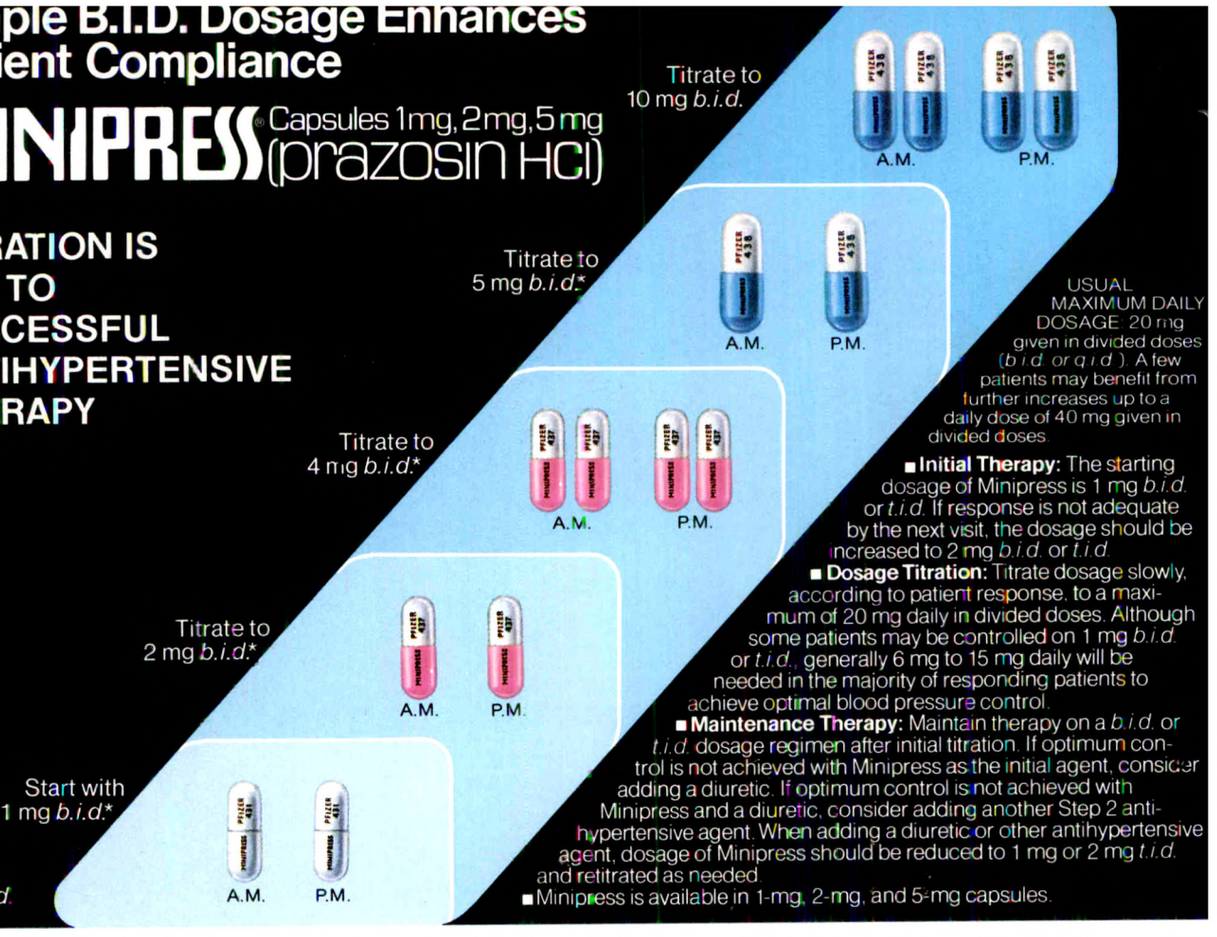
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- **Initial Therapy:** The starting dosage of Minipress is 1 mg *b.i.d.* or *t.i.d.* If response is not adequate by the next visit, the dosage should be increased to 2 mg *b.i.d.* or *t.i.d.*
- **Dosage Titration:** Titrate dosage slowly, according to patient response, to a maximum of 20 mg daily in divided doses. Although some patients may be controlled on 1 mg *b.i.d.* or *t.i.d.*, generally 6 mg to 15 mg daily will be needed in the majority of responding patients to achieve optimal blood pressure control.
- **Maintenance Therapy:** Maintain therapy on a *b.i.d.* or *t.i.d.* dosage regimen after initial titration. If optimum control is not achieved with Minipress as the initial agent, consider adding a diuretic. If optimum control is not achieved with Minipress and a diuretic, consider adding another Step 2 antihypertensive agent. When adding a diuretic or other antihypertensive agent, dosage of Minipress should be reduced to 1 mg or 2 mg *t.i.d.* and retitrated as needed.
- Minipress is available in 1-mg, 2-mg, and 5-mg capsules.

BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

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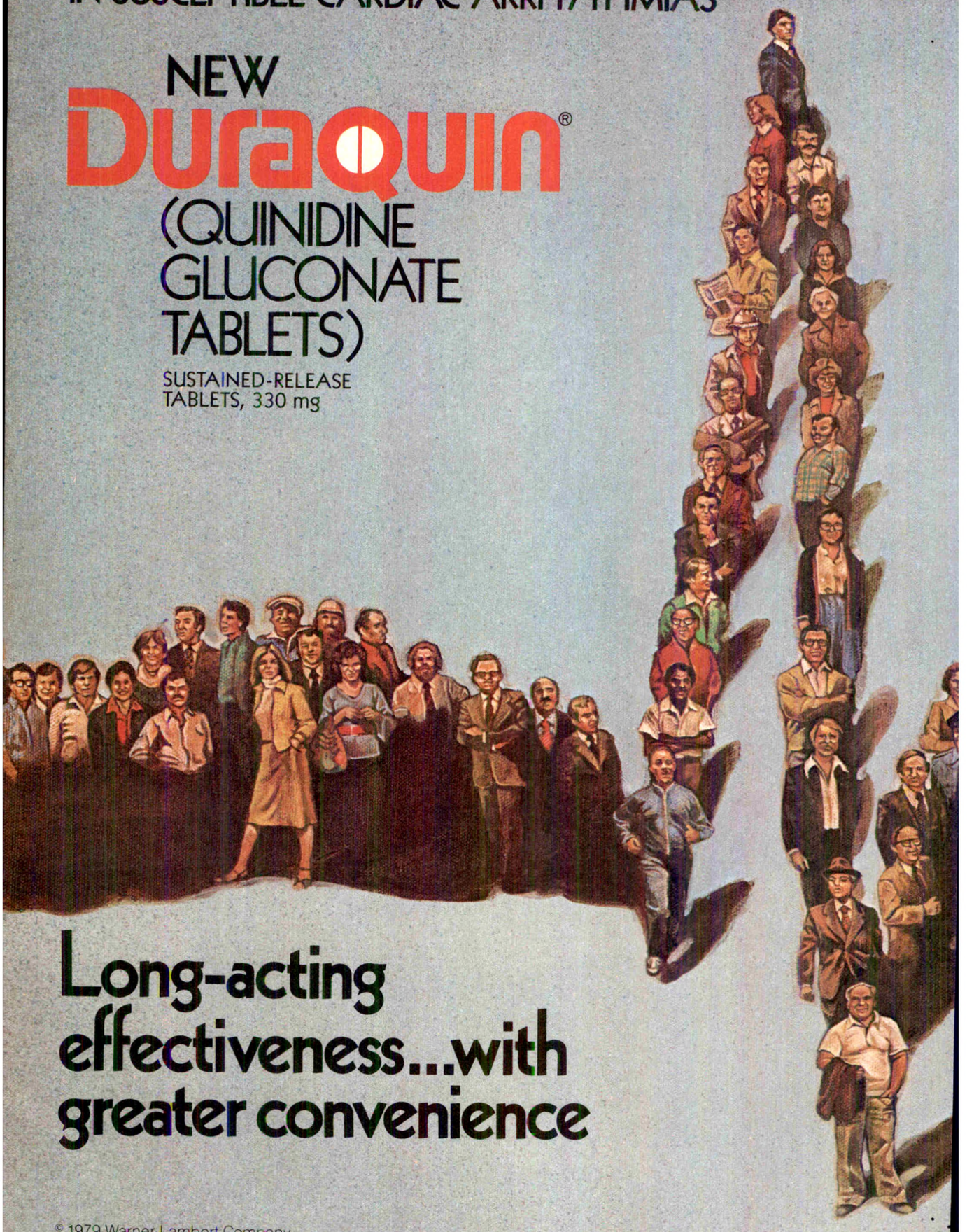
IN SUSCEPTIBLE CARDIAC ARRHYTHMIAS

NEW

Duraquin®

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SUSTAINED-RELEASE
TABLETS, 330 mg



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*The quantity of drug and frequency of administration needed to achieve desired clinical results must be determined for each patient.
†Red Book, 1979.



Duraquin®
(QUINIDINE GLUCONATE TABLETS)
sustained-release tablets, 330 mg

Brief summary of prescribing information
DURAQUIN® (quinidine gluconate tablets) Sustained Release
CLINICAL PHARMACOLOGY: In clinical studies, single doses of Duraquin produced a mean maximum plasma level at 2 hours which was maintained for 12 hours. This broad plateau indicates slow, continuous absorption from the gastrointestinal tract.

In multiple dose studies, administration of Duraquin tablets, 660 mg every 12 hours, produced steady state (equilibrium) plasma levels shortly after 24 hours. The average quinidine plasma levels (Cramer and Isaksson assay [1]) were 0.81 mcg/ml and the mean peak levels were 1.16 mcg/ml in a group of normal male subjects weighing 75 Kg. Following the last dose at steady state, quinidine plasma levels decreased at an approximate rate of 50% in 10 hours. This compares to the expected plasma half-life of 6.3 hours for quinidine sulfate tablets, USP.

Therapeutic and toxic effects coordinate better with plasma levels than with dosage. While therapeutic levels of 3 to 6 mcg/ml with a range of 1.5 to 9 mcg/ml have been reported, these values are based on peak plasma levels determined by the less specific Edgar and Sokolow assay [2] This procedure yields quinidine levels averaging 22% higher than the Cramer and Isaksson assay. Plasma levels vary considerably in patients receiving identical doses. Therefore, it is advisable to adjust the dosage by monitoring plasma quinidine levels.

INDICATION: Duraquin tablets are indicated for the prevention of premature atrial, nodal, or ventricular contractions. They are also indicated for the maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion of atrial, nodal, or ventricular tachycardia, atrial flutter and fibrillation (either paroxysmal or chronic).

[1]Cramer, G. and Isaksson, B. Quantitative Determination of Quinidine in Plasma. Scandinavian J. Clin. & Lab. Investigation 15, 553, 1963.
[2]Edgar, A.L. and Sokolow, M. Experiences with the Photofluorometric Determination of Quinidine in Blood. J. Lab. Clin. Med. 36, 478, 1950.

CONTRAINDICATIONS: 1. History of hypersensitivity to quinidine manifested by thrombocytopenia, skin eruption, febrile reactions, etc.
2. Complete A-V block.
3. Complete bundle branch block or other severe intraventricular conduction defects exhibiting marked QRS widening or bizarre complexes.
4. Myasthenia gravis.
5. Arrhythmias associated with digitalis toxicity.

WARNINGS: 1. (a) In the treatment of atrial fibrillation with rapid ventricular response, ventricular rate should be controlled with digitalis glycosides *prior* to administration of quinidine.
(b) In the treatment of atrial flutter with quinidine, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine.

Recent reports have described increased, potentially toxic, digoxin plasma levels when quinidine is administered concurrently. When concurrent use is necessary, digoxin dosage should be reduced and plasma concentration should be monitored and patients observed closely for digitalis intoxication.

2. Quinidine cardiotoxicity may be manifested by increased PR and QT intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia. Appearance of these toxic signs during quinidine administration mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. Note: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia.
3. "Quinidine Syncope" may occur as a complication of long-term therapy. It is manifested by sudden loss of consciousness and ventricular arrhythmias with bizarre QRS complexes. This syndrome does not appear to be related to dose or plasma levels but occurs more often with prolonged QT intervals.

Brief summary continued on following page.

PD-JA-2299-1-P (3-79)

PARKE-DAVIS

PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, NJ 07950

Duraquin®
(QUINIDINE GLUCONATE TABLETS) sustained-release tablets, 330 mg

Brief summary continued from previous page.

4. Because quinidine antagonizes the effect of vagal excitation upon the atrium and the A-V node, the administration of parasympathomimetic drugs (choline esters) or the use of any other procedure to enhance vagal activity may fail to terminate paroxysmal supraventricular tachycardia in patients receiving quinidine.
5. Quinidine should be used with extreme caution in:
a) The presence of incomplete A-V block, since a complete block and asystole may result. Quinidine may cause unpredictable abnormalities of rhythm in digitalized hearts. Therefore, it should be used with caution in the presence of digitalis intoxication (see 1. (b) above).
b) Partial bundle branch block.
c) Severe congestive heart failure and hypotensive states due to the depressant effects of quinidine on myocardial contractility and arterial pressure.
d) Poor renal function, especially renal tubular acidosis, because of the potential accumulation of quinidine in plasma leading to toxic concentrations.

PRECAUTIONS:

1. Test Dose—A preliminary test dose of a single tablet of quinidine *sulfate* should be administered prior to the initiation of the sustained release gluconate to determine whether the patient has an idiosyncrasy to the Quinidine molecule.

2. Hypersensitivity—During the first weeks of therapy, hypersensitivity to quinidine, although rare, should be considered (eg, angioedema, purpura, acute asthmatic episode, vascular collapse).

3. Long-Term Therapy—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy and the drug should be discontinued if blood dyscrasias or signs of hepatic or renal disorders occur.

4. Large Doses—ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered.

5. Usage in Pregnancy—The use of quinidine, in pregnancy, should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus.

6. Nursing Mothers—The drug should be used with extreme caution in nursing mothers because the drug is excreted in breast milk.

7. General—In patients exhibiting asthma, muscle weakness, and infection with fever *prior* to quinidine administration, hypersensitivity reactions to the drug may be masked.

DRUG INTERACTIONS:

1. Caution should be used when quinidine and its analogs are administered concurrently with coumarin anticoagulants. This combination may reduce prothrombin levels and cause bleeding.
2. Quinidine, a weak base, may have its half-life prolonged in patients who are concurrently taking drugs that can alkalize the urine, such as thiazide diuretics, sodium bicarbonate, and carbonic anhydrase inhibitors. Quinidine and drugs which alkalize the urine should be used together cautiously.
3. Quinidine exhibits a distinct anticholinergic activity in the myocardial tissues. An additive vagolytic effect may be seen when quinidine and drugs having anticholinergic blocking activity are used together. Drugs having cholinergic activity may be antagonized by quinidine.
4. Quinidine and other antiarrhythmic agents may produce additive cardiac depressant effects when administered together.
5. Quinidine interaction with cardiac glycosides (digoxin). See WARNINGS.
6. Antacids may delay absorption of quinidine but appear unlikely to cause incomplete absorption.
7. Phenobarbital and phenytoin may reduce plasma $t_{1/2}$ of quinidine by 50%.
8. Quinidine may potentiate the neuromuscular blocking effect in ventilatory depression of patients receiving decamethonium, tubocurare, or succinylcholine.

ADVERSE REACTIONS: Symptoms of cinchonism (ringing in the ears, headache, disturbed vision) may appear in sensitive patients after a single dose of the drug.

Gastrointestinal: The most common side effects encountered with quinidine are referable to this system. Diarrhea frequently occurs, but it rarely necessitates withdrawal of the drug. Nausea, vomiting, and abdominal pain also occur. Some of these effects may be minimized by administering the drug with meals.

Cardiovascular: widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardias and fibrillation; paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.

CNS: headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata); optic neuritis.

Dermatologic: cutaneous flushing with intense pruritus.

Hypersensitivity reactions: angioedema, acute asthmatic episode, vascular collapse, respiratory arrest.

DOSAGE AND ADMINISTRATION: Dosage should be titrated to give the desired clinical effect, e.g., elimination of paroxysmal rhythm or reduction in premature contractions (See CLINICAL PHARMACOLOGY). This will often require prolonged ambulatory ECG monitoring, as hour-to-hour variability renders brief ECG recordings unreliable. When doses larger than 2.5 g/day are used, quinidine blood levels should be monitored, if possible, and serial ECGs should be followed (See WARNINGS and PRECAUTIONS).

For prevention of premature contractions and maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion, the usual dosage is from 330 mg to 660 mg every eight hours, most patients requiring the higher dose.

In elderly patients, and in patients in the lower end of the normal weight range, plasma quinidine determinations should be considered. Dosage adjustments may be required.

OVERDOSAGE: Cardiotoxic effects of quinidine may be reversed in part by molar sodium lactate; the hypotension may be reversed by vasoconstrictors and by catecholamines (since the vasodilation is partly due to alpha-adrenergic blockade).

HOW SUPPLIED: N 0071-0850 (P-D 850) Duraquin (quinidine gluconate tablets) 330-mg tablets are supplied in bottles of 100 tablets.

AHFS Category 24:04

YD

PARKE-DAVIS

Division of Warner-Lambert Company
Morris Plains, NJ 07950

SEARLE

Aldactazide®

(spironolactone 25 mg./ hydrochlorothiazide 25 mg.)

WARNING

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see ***Warnings***). Aldactazide should be used only in those conditions described in the ***Indications*** section of the complete prescribing information. Unnecessary use of this drug should be avoided.

Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edma is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist.

Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia.

Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions:

Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established.

Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness.

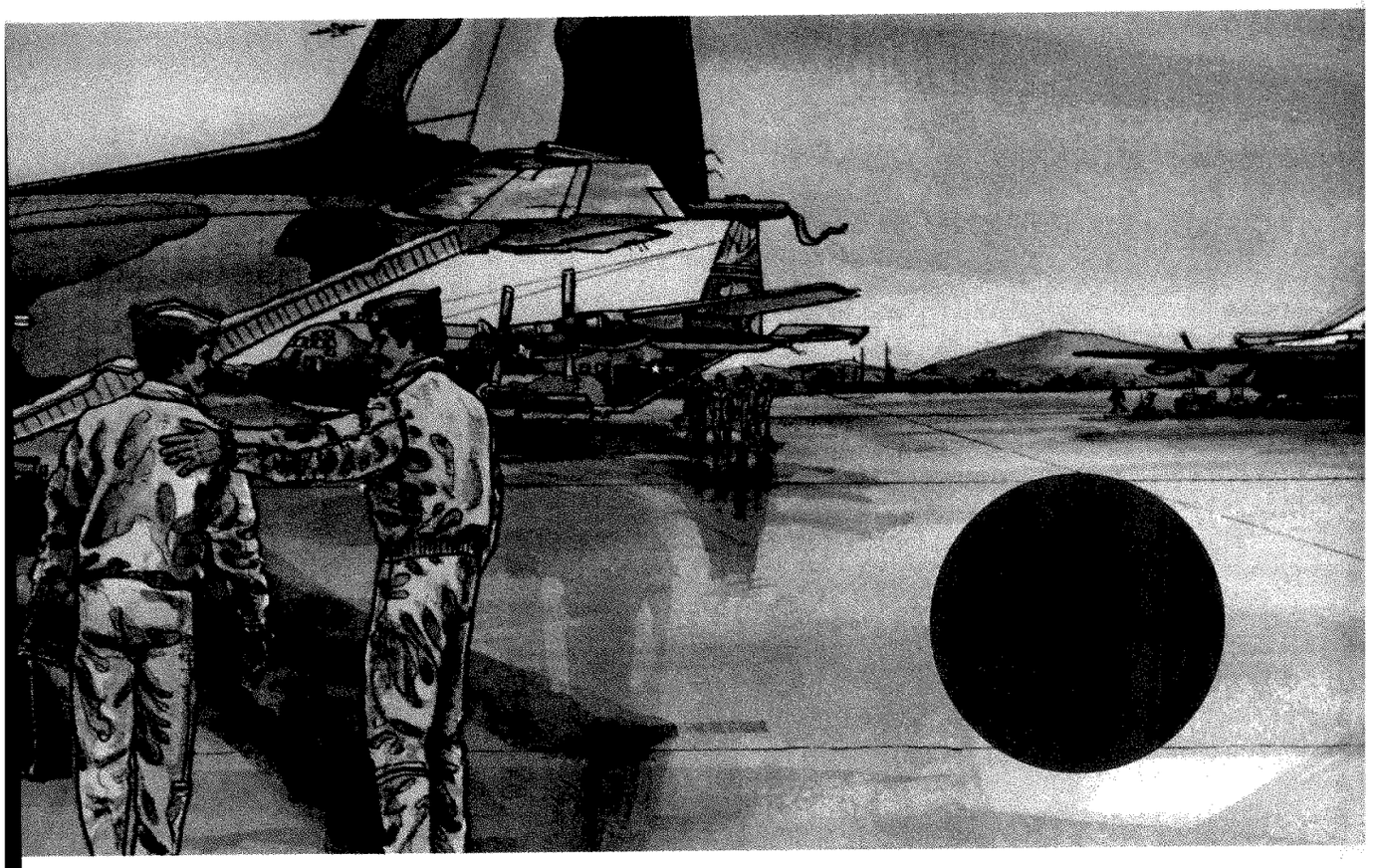
Adverse reactions are usually reversible upon discontinuation of Aldactazide.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to:
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Medical Communications Department
Box 5110
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911-1

No longer grounded by hypertension... No longer grounded by the side effects of therapy.



The majority of 32 USAF aircrewmen with elevated blood pressure failed to respond adequately to therapy with a thiazide diuretic.[1]

For these 32 patients, therapy with Aldactazide® (spironolactone 25 mg./hydrochlorothiazide 25 mg.)* produced a 94% efficacy rate in blood-pressure control†—as well as an absence of orthostatic hypotension and sedation which could compromise flying safety—84% returned to flying duty.

Additive antihypertensive action

Aldactazide is the only potassium-sparing combination of diuretics with additive action; that is, both components are consistently effective antihypertensive agents. The two diuretic agents in Aldactazide have different but complementary mechanisms and sites of action to provide additive antihypertensive effects. Aldactazide has been shown to be more effective in reducing blood pressure than either of its components used alone.

Limitations to consider:

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Thus, Aldactazide should be prescribed only when other measures are considered inadequate or inappropriate. Fixed-dose combination drugs are not indicated for initial therapy. (See boxed warning and *Warnings* section of Aldactazide prescribing information.)

SEARLE

Aldactazide®

(spironolactone 25 mg./hydrochlorothiazide 25 mg.)

Effective long-term hypertension therapy when other measures are considered inadequate or inappropriate.

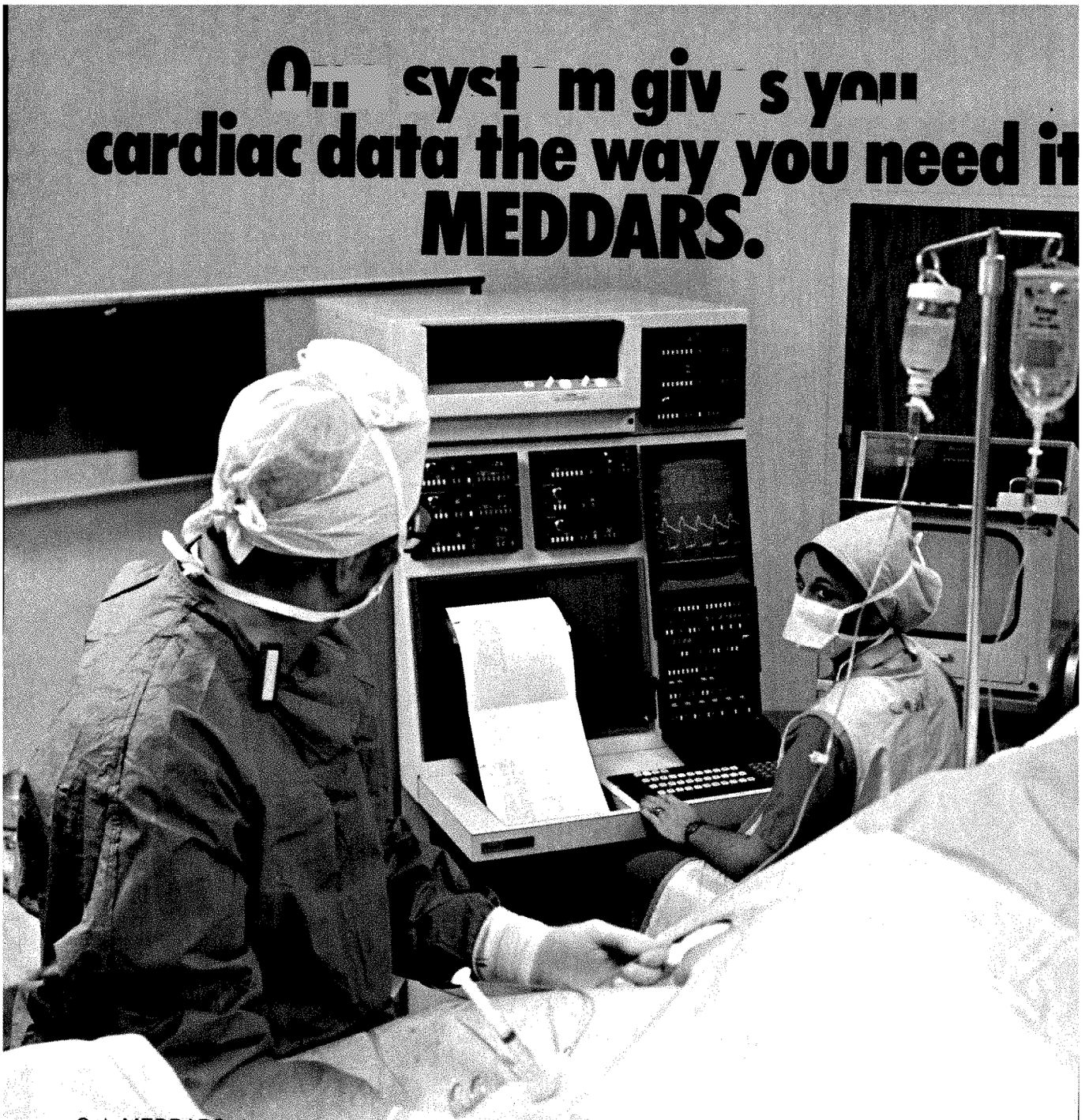
1. Hull, D. H., and others: Treatment of Hypertension in Aviators: A Clinical Trial With Aldactazide, Aviat. Space Environ. Med. 49:503-511 (March) 1978.

* While nondiuretic antihypertensive medications should be considered for the general hypertensive population unresponsive to thiazides, USAF determined that the demands placed on crewmembers of high-performance aircraft made these therapies inappropriate.

† The authors suggest that the high success rate in this particular study may have been due to the relative mildness of their patients' hypertension and to their concurrent adoption of corrective physiological measures.

Before prescribing Aldactazide, please consult the complete prescribing information, a brief summary of which is on the facing page.

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INDICATIONS:

Congestive heart failure: Congestive heart failure, all degrees, is the primary indication. The increased cardiac output due to digoxin results in diuresis and general amelioration of the disturbances characteristic of right (venous congestion, edema) and left (dyspnea, orthopnea, cardiac asthma) heart failure.

Digoxin, generally, is most effective in "low output" failure and less effective in "high output" (bronchopulmonary insufficiency, infection, hyperthyroidism) heart failure.

Digoxin should be continued after heart failure is abolished unless some known precipitating factor is corrected.

Atrial fibrillation: Atrial fibrillation, especially when the ventricular rate is elevated. Digoxin rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

Atrial flutter: Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digoxin at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digoxin if failure ensues or if atrial flutter is a frequent occurrence.

Paroxysmal atrial tachycardia: Oral digoxin may be used, especially if the condition is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if heart failure has ensued or paroxysms recur frequently, digoxin should be maintained by oral administration.

Digoxin is not indicated in sinus tachycardia unless due to heart failure.

Cardiogenic shock: The drug is often employed, especially when the condition is accompanied by pulmonary edema. Digoxin seems to affect adversely shock due to septicemia from gram-negative bacteria.

CONTRAINDICATIONS: The presence of toxic effects (see ADVERSE REACTIONS section) induced by any digitalis preparation is a contraindication to all of the glycosides.

Allergy, though rare, does occur. It may not extend to all preparations, and another may be used.

Ventricular fibrillation.

WARNINGS:

Digitalis alone or with other drugs has been promoted for use in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

Many of the arrhythmias for which digoxin is advised closely resemble those reflecting digoxin toxication. If the possibility of digoxin intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digoxin intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

Patients with renal insufficiency require smaller than usual doses of digoxin. Newborn infants display considerable variability in their tolerance to digoxin, depending on their degree of maturity.

Premature and immature infants are particularly sensitive, and dosage must be reduced and digitalization should be even more individualized and cautiously approached than in more mature infants. Impaired renal function must also be carefully taken into consideration.

Congestive heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. A relatively low total dose administered in divided doses and concomitant use of antihypertensive drugs has been recommended. ECG monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with rheumatic carditis, especially when severe, are unusually sensitive to digoxin and prone to disturbances of rhythm. If heart failure develops, digitalization may be initiated with relatively low doses; then it can be cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS: Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid digoxin toxicity if digoxin is used to help the arrhythmia.

Digoxin is not indicated for the treatment of ventricular tachycardia unless congestive heart failure supervenes after a protracted episode not itself due to digoxin.

Potassium depletion sensitizes the myocardium to digoxin and toxicity may develop even with normal dosage. Hypokalemia may also alter the rate of onset and intensity of the positive inotropic effect of digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin.

Potassium wastage may result from diuretic or corticosteroid therapy, hemodialysis, and from excretion of gastrointestinal secretions. It may accompany malnutrition, diarrhea, prolonged vomiting, sprue, and long-standing congestive heart failure. In general, rapid changes in serum potassium or other electrolytes are to be avoided, and intravenous treatment with potassium should be reserved only for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES section).

Patients with acute myocardial infarction, severe pulmonary disease, or far advanced heart disease may be more sensitive to digoxin and more prone to disturbances of rhythm.

Calcium affects contractility and excitability of the heart in a manner similar to that of digoxin. Calcium may produce serious arrhythmias in digitalized patients.

In myxedema, the digoxin requirements are less because excretion rate is decreased and blood levels are significantly higher.

In incomplete A-V block, especially in patients subject to Stokes-Adams attacks, advanced or complete heart block may develop if digoxin is given. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.

Patients with chronic constrictive pericarditis may respond unfavorably to digoxin.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Renal insufficiency delays the excretion of digoxin and dosage must be adjusted accordingly in patients with renal disease. Note: This applies also to potassium administration should it become necessary.

Electrical conversion of arrhythmias may require reduction of digoxin dosage.

Dosage must be carefully titrated and differences in the bioavailability of parenteral preparations, elixir, and tablets should be taken into account when switching patients from one preparation to another.

Electrocardiographic monitoring may be necessary to avoid intoxication.

Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

ADVERSE REACTIONS:

Gynecomastia: Uncommon.

Overdose or toxic effects in adults:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea are the most common early symptoms of overdosages in the adult (but rarely conspicuous in infants). Uncontrolled heart failure may also produce such symptoms.

Central nervous system: Visual disturbances (blurred vision, yellow vision), headache, weakness, apathy.

Cardiac disturbances (arrhythmias): Ventricular premature beats are the most common, except in infants and young children. Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (interference) dissociation and paroxysmal atrial tachycardia (PAT) with block are also common arrhythmias due to digoxin overdosage.

Conduction disturbances: Excessive slowing of the pulse is a clinical sign of digoxin overdosage. Atrioventricular block of increasing degree may proceed to complete heart block. Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac toxic disturbances. Digoxin may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

Overdose or toxic effects in children:

Toxic signs differ from the adult in a number of respects. Cardiac arrhythmias are the more reliable and frequent signs of toxicity.

Vomiting and diarrhea, neurologic and visual disturbances are rare as initial signs.

Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.

Atrial arrhythmias, atrial ectopic rhythms, and paroxysmal atrial tachycardia with A-V block particularly are more common manifestations of toxicity in children.

Ventricular arrhythmias are rare.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE: Digoxin should be discontinued until all signs of toxicity are abolished. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.

Potassium salts are commonly used. Potassium chloride in divided oral doses totaling 4-6 grams for adults (see PEDIATRIC INFORMATION section for pediatric dosage) may be given provided renal function is adequate.

When correction of the arrhythmia is urgent and the serum potassium level is low or normal, potassium should be administered intravenously in a solution of 5 percent dextrose in water. A total of 40-100 milliequivalents (30 milliequivalents per 500 milliliters) is given at the rate of 20 milliequivalents per hour unless limited by pain due to local irritation.

Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.

Continuous electrocardiographic monitoring should be performed to watch for any evidence of potassium toxicity, e.g., peaking of T waves, and to observe the effect on the arrhythmia so that the infusion may be promptly stopped when the desired effect is achieved.

Caution: Potassium should not be used and may be dangerous for severe or complete heart block due to digoxin and not related to any tachycardia.

Other agents that have been approved for the treatment of digoxin intoxication include procainamide, lidocaine, and propranolol.

Pediatric Information: (See adult section for other recommendations for the treatment of arrhythmias produced by overdosages and for additional recommendations and cautions regarding the use of potassium.) Potassium preparations may be given orally in divided doses totaling 1-1.5 milliequivalents/kilogram (1 gram K contains 13.4 milliequivalents). When correction of the arrhythmia is urgent, approximately 0.5 milliequivalents/kilogram of potassium per hour may be given, with careful electrocardiographic monitoring, as a solution of 20 milliequivalents or less for 500 milliliters in 5 percent dextrose in water. The total dose should generally not exceed 2 milliequivalents of potassium/kilogram.

DOSAGE AND ADMINISTRATION: Oral digoxin is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. The amount can be predicted approximately from the lean body mass of the patient with allowances made for excretion during the time taken to induce digitalization.

Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.

Recommended dosages are practical average figures that may require considerable modification as dictated by individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended or average doses. (See WARNINGS and PRECAUTIONS sections.)

The average amount of digoxin that patients must accumulate to be digitalized with digoxin tablets is 1.0-1.5 milligrams. Digitalization may be accomplished by any of several approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount accumulated.

In previously undigitalized patients, a single loading dose of 0.5-0.75 milligram orally usually produces a detectable effect in 1-2 hours that becomes maximal in 6-8 hours. Additional doses of 0.25-0.5 milligram may be given cautiously at 6-8 hour intervals to full digitalization.

In previously undigitalized patients, institution of daily maintenance therapy (0.125-0.5 milligram, see next paragraph) without a loading dose results in development of steady-state plateau concentrations in about 7 days in patients with normal renal function.

The average daily oral maintenance dose is 0.125-0.5 milligram, usually 0.25 milligram. In the elderly patient, 0.125-0.25 milligram should be considered the average maintenance dose.

In patients with renal impairment, digoxin excretion is impaired and serum half-life is prolonged. Digitalizing and maintenance doses are lower than those recommended for patients with normal renal functions. Signs of digoxin toxicity develop sooner in patients with renal impairment, and it takes longer for toxic signs and symptoms to disappear. Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state plateau in patients with renal impairment than in patients with normal renal function.

It cannot be overemphasized that the values given are averages and substantial individual variation can be expected.

Children: Digitalization must be individualized. Generally, premature and immature infants are particularly sensitive, requiring reduced dosage that must be determined by careful titration.

Oral Dosage. Beyond the immediate newborn period, children require proportionally greater doses than adults on the basis of body weight or surface area. The recommended oral digitalizing dosages in children with normal renal function are:

Newborn infants (normal), up to 1 month, require 40-60 micrograms (mcg)/kilogram.

Infants, 1 month to 2 years, require approximately 60-80 micrograms (mcg)/kilogram.

Children, 2 years to 10 years, require 40-60 micrograms (mcg)/kilogram.

Children, over 10 years of age, require adult dosages in proportion to their body weight.

Maintenance therapy is 20-30 percent of the digitalizing dose administered each day.

Long term use of digoxin is indicated in almost all infants who have been digitalized for acute congestive heart failure unless the cause is transient. Many favor maintaining digoxin until at least 2 years of age in all infants with paroxysmal atrial tachycardia or in those who show either definite or latent failure.

Many children with severe inoperable congenital defects need digoxin throughout childhood and often for life.

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CLINICAL STUDIES

Medically Refractory Unstable Angina Pectoris. I. Long-Term Follow-up of Patients Undergoing Intraaortic Balloon Counterpulsation and Operation

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Of 82 patients with medically refractory unstable angina pectoris seen between October 1972 and January 1978, 60 patients underwent a combination of intraaortic balloon pump counterpulsation, cardiac catheterization and coronary revascularization. Most patients had atherosclerotic involvement of the vessels of the anterior left ventricular wall, 48 patients (80 percent) had abnormalities of left ventricular wall contraction and 22 patients (36 percent) had evidence of acute myocardial injury. One operative and one late death occurred. The perioperative infarction rate was 5 percent. Survivors, followed up for 3 to 63 months (mean 31 months), have done remarkably well; 77 percent are considered employable, and more than 90 percent are in functional class I or II.

Despite earlier reports to the contrary, patients with unstable angina pectoris have tolerated angiography and coronary bypass graft surgery with low morbidity and mortality rates.[1–6] Although some studies[7,8] indicate that the short-term mortality may be similar for both medically and surgically treated patients, other data suggest that the long-term morbidity and mortality of these patients can be decreased by operation.[9] This review of our clinical experience was undertaken to assess the long-term outlook for patients with unstable angina *refractory to medical treatment* who have undergone bypass operations on an urgent basis.

Methods

Patients: From October 1972 through January 1978, a total of 82 patients at the Beth Israel Hospital underwent attempted intraaortic balloon pump insertion for medically refractory unstable angina. All patients had angina decubitus for 48 hours or more within an intensive care unit setting. Chest pain was accompanied by transient electrocardiographic S-T changes and was unresponsive to an optimal medical program consisting of administration of propranolol for maximal beta adrenergic blockade (resting pulse below 60/min), if not contraindicated, and administration of nitrate (to a systolic blood pressure of less than 105 mm Hg) in the form of sublingual nitroglycerin, isosorbide dinitrate or nitroglycerin ointment. Electrocardiograms and serum enzyme de-

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terminations were obtained daily. A prior myocardial infarction, however recent, was not a sufficient criterion for exclusion from the protocol if the patient continued to have episodes of unstable angina as defined.

Angiography and surgery: Within 24 hours of the institution of counterpulsation, coronary and left ventricular angiography was performed using previously described techniques,[10] and coronary bypass graft surgery was performed within 72 hours of balloon insertion. A bubble oxygenator was primed with Ringer's lactate solution, 5 percent dextrose in water, and albumin, and a roller pump was used. One or two proximal aortosaphenous anastomoses for grafts were usually constructed before cardiopulmonary bypass was begun. Moderate hypothermia (25° to 28°C) and left ventricular venting were utilized in all patients. The heart was continuously bathed with cold (approximately 5°C) Ringer's lactate solution, which obviated the need for electrically induced fibrillation. The aorta was cross-clamped infrequently, and then only for short periods of time. All distal anastomoses were carried out with a combination of interrupted and continuous 7-0 Tevdek® or Prolene® sutures. Mechanical coronary endarterectomy of the left anterior descending artery and right coronary artery was performed when indicated.

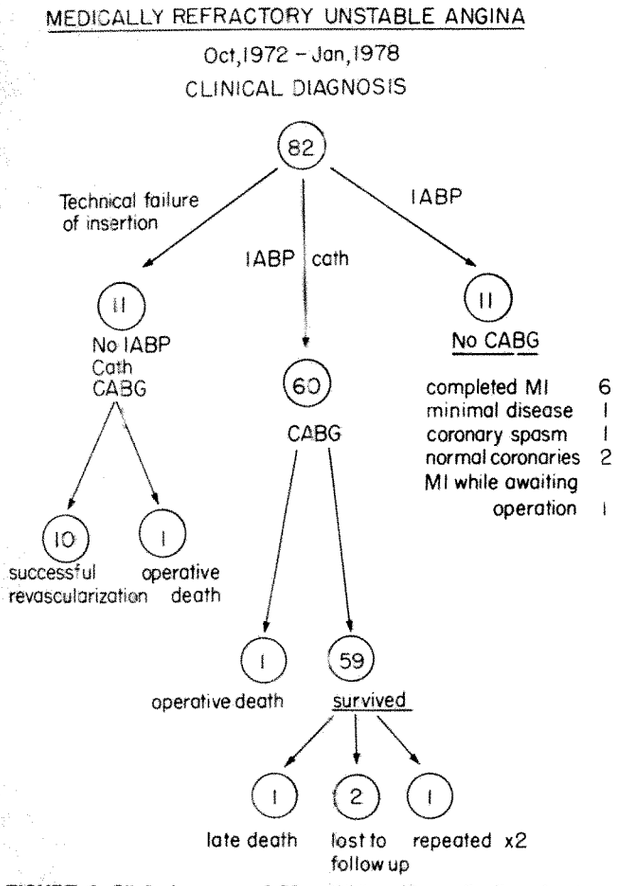


FIGURE 1. Clinical course of 82 patients with medically refractory angina pectoris selected for intraaortic balloon pumping (IABP). CABG = coronary bypass grafting; cath = cardiac catheterization and left ventricular and coronary angiography; IAPB = intraaortic balloon pump; MI = myocardial infarction. One patient is now doing well after surviving operation (repeated X2), catheterization, angiography and intraaortic balloon pumping, a second operation 9 months later (a new lesion in a previously unaffected coronary artery) and a third operation 3 years later (graft stenosis).

Results

Patients satisfying criteria for medically refractory unstable angina (Fig. 1): Eighty-two patients fulfilled our criteria for medically refractory unstable angina pectoris. In 11 patients, the intraaortic balloon pump could not be inserted. All of these patients underwent cardiac catheterization and coronary bypass grafting. There was one operative death. Another 11 patients underwent counterpulsation without subsequent cardiac surgery. In six of these patients, a myocardial infarction had occurred immediately before insertion of the intraaortic balloon pump, and the patients were successfully weaned from counterpulsation without further angina. One patient had coronary spasm only, and one patient whose operation was delayed sustained an acute myocardial infarction 48 hours after cardiac catheterization. One patient had minimal coronary disease, and two had normal coronary arteries.

The remaining 60 patients who underwent counterpulsation, cardiac catheterization and cardiac surgery ranged in age from 32 to 76 years (mean 52). There were 44 men and 16 women. Fifty percent of the patients had multiple risk factors for premature coronary artery disease; heavy cigarette smoking was the most commonly encountered single risk factor (73 percent).

Results of medical management (Table I): All 60 patients were treated with strict bed rest within the medical intensive care unit. The amount of time spent by patients in our unit before insertion of the balloon pump was 4.5 ± 3.5 days (mean ± standard deviation) but ranged from 1 to 21 days. Maximal medical therapy included administration of nitrates, morphine and propranolol in all patients without contraindications. Some patients received no propranolol because of the presence of congestive heart failure, hypotension or bradycardia. In those receiving propranolol, the mean dose was 144 mg/day, but individual dosage ranged widely, from 2 mg (given intravenously) to 800 mg/day.

TABLE I

Medical Management of 60 Patients With Medically Refractory Unstable Angina

	Patients	
	no.	%
Patients not receiving propranolol (no.)	9	15
Contraindications		
CHF	4	
MR	2	
Asthma	1	
Severe diabetes	1	
None	1	
Patients treated with propranolol	51	85
Dose (mg/day)		
Mean ± SD	144 ± 153	
Range	2 – 800	
Minimal heart rate (beats/min)	56 ± 8	

The mean minimal heart rate achieved in these patients was 56 ± 8 beats/min, and all patients achieved a heart rate of well under 70 beats/min.

Effect of counterpulsation: The effect of counterpulsation on recurrent myocardial ischemia was dramatic in most cases. Ninety-five percent of patients had complete or partial relief of chest pain, and only three patients had no change in symptoms. In the latter patients, operation was performed promptly.

Angiographic findings (Table II): After insertion of the intraaortic balloon pump the 60 patients underwent cardiac catheterization and angiography, usually within 12 hours. The number of patients with one, two and three vessel disease was approximately equal; however, 58 of the 60 patients (97 percent) had significant atherosclerosis of the vessels supplying the anterior left ventricular wall, and 80 percent had left ventricular wall motion abnormalities.

Antecedent myocardial infarction: Twenty-two patients (37 percent) had electrocardiographic evidence of an old myocardial infarction, and 22 had a new myocardial infarction as evidenced by the electrocardiogram, serum enzyme changes or gross findings at operation. Of these, 7 patients (12 percent) had evidence of both old and new infarction. Twenty-three patients (38 percent) had neither old nor new infarction. In the patients with acute myocardial injury the interval between the acute infarction, which was the immediate cause of hospitalization in many cases, and the insertion of the balloon was 8.5 ± 6 days (range 2 to 21 days).

Clinical-anatomic correlations (Table III): The patients manifested three clinical-anatomic patterns. Nineteen patients had ischemia in the area of one critically stenosed vessel, 19 had advanced multivessel disease and the remaining 22 had an acute myocardial injury. Among the latter group, there were two clear patterns. The majority, 17, had small repetitive infarctions in the area of one vessel, whereas 5 had had acute completed infarction in the area of one vessel with new threatened ischemia in the area of a second vessel. The majority of the 60 patients had at least one vessel with a high degree of stenosis, delayed progression of contrast material down the involved vessel and a lack of collateral circulation to the area in jeopardy.

Operations performed: Twenty-three patients (38 percent) had a single coronary bypass graft, 22 (37 percent) had two grafts and 15 (25 percent) had three or four grafts. Four patients (6 percent) had concomitant mitral valve replacement, one of whom also had a simultaneous carotid endarterectomy.

Complications of intraaortic balloon pump (Table IV): Five patients (60 percent) of the entire group of 82 patients who underwent attempted intraaortic balloon pump insertions for medically refractory preinfarction angina had serious complications consisting of dissection, deep sepsis involving the side arm Dacron® graft or, in one case, myocardial infarction that occurred while the patient was awaiting operation. Another five patients (6 percent) had lesser but still significant complications of local embolus, thrombus or superficial sepsis. In another 11 patients (13 percent) the intraaortic balloon pump could not be inserted.

Morbidity and mortality of coronary bypass operation (Table V): Among the 60 patients undergoing both counterpulsation and cardiac operation, 3 (5 percent) had an asymptomatic intraoperative myocardial infarction, as indicated by a review of pre- and postoperative electrocardiograms. In another seven patients (12 percent) the results of surgery were unsatisfactory: One patient died intraoperatively, one died suddenly 7 months after operation, three had known demonstrated late myocardial infarction and two had concomitant myocardial infarction and angiographically demonstrated graft closure within 14 days of operation. Because early graft closure is likely to result in symptomatic infarction in patients with unstable angina, we now recommend that all such patients have emergency graft angiography if ischemic pain recurs in the immediate postoperative period.

Long-term clinical results: The patients were followed up for 3 to 63 months (mean 31 ± 16 months), in most cases personally and, when this was not possible, by questionnaire to the referring physician. Two pa-

TABLE II

Angiographic Findings in 60 Patients With Medically Refractory Unstable Angina

	Patients	
	no.	%
Coronary artery disease		
Vessels affected		
RCA	30	50
LCx	28	47
LAD	52	96
Main left	6	
no. of vessels affected*		
One	19 (LAD in 17)	32
Two	22	36
Three	19	32
LV wall motion abnormality		
None	12	20
Ant wall	30	50
Inf wall	5	8
Ant and inf wall	13	22

* Left main coronary artery counted as two vessel disease.

Ant = anterior; Inf = inferior; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricular; RCA = right coronary artery.

TABLE III

Anatomic Patterns in 60 Patients With Medically Refractory Unstable Angina

Type	Pattern	Patients no.	Patients %
I	One vessel ischemia	19	32
II	Multivessel advanced disease	19	32
IIIA	Small repetitive infarcts in area of one vessel	17	28
IIIB	Completed acute infarction, with ischemia in new area	5	8

TABLE IV

Complications in Total Group of 82 Patients Undergoing Attempted Intraaortic Balloon Pump Insertions for Medically Refractory Unstable Angina

	no.	Incidence Rate (%)
Serious IABP complications		
Dissection	1	
Deep sepsis*	3	
MI on IABP	1	
Total	5	6
Other IABP complications		
Local embolus or thrombus	3	
Superficial sepsis	2	
Total	5	6
Inability to insert IABP	11	13

* Infections requiring excision of sidearm Dacron graft or bypass outside normal course of the native vessel.
IABP = intraaortic balloon pump; MI = myocardial infarction.

TABLE V

Unsatisfactory Outcomes in 60 Patients With Medically Refractory Unstable Angina Undergoing Coronary Bypass Surgery

Outcome	Patients no.	Patients %
Intraoperative death	1	1.6
Late death	1	1.6
Early (7–14 days) graft closure and infarction	2	3
Late (>6 months) infarction	3	5
Total	7	12

tients were lost to long-term follow-up, one patient died in the operating room and one died late. Of the remaining 56 patients, 43 (77 percent) required no further hospitalization; 30 of these (54 percent) were currently employed and another 13 (23 percent) were thought to be employable.

Patients were also assessed as to New York Heart Association functional classification.[11] Fifty-two (93 percent) of the 56 patients in the follow-up group are in functional class I or II, although one of these has required two reoperations (Fig. 1). Four patients (7 percent) are in class III and none are in class IV (Fig. 2). Three patients with documented graft closure and infarction have remained in class II.

Discussion

Definition of unstable angina: The considerable variation in mortality rates among early reported studies of patients with unstable angina may have been due to a lack of anatomic data and a failure to achieve general agreement concerning the definition of this syndrome. The latter has resulted in a multiplicity of names for unstable anginal syndromes: unstable angina, preinfarction angina, intermediate syndrome and crescendo angina. In a well documented long-term follow-up study of patients with preinfarction angina, Gazes et al.[12] described a group of "high risk" patients with angina decubitus, transient electrocardiographic changes and unresponsiveness to medical management which at that time did not include drug treatment to provide beta adrenergic blockade. In that group, the immediate hospital mortality rate was 18 percent, the 1 year mortality rate 43 percent and the 2 year mortality rate greater than 50 percent. Since that report, there has been a gradual agreement regarding the definition of unstable angina. In general, this definition matches that of their high risk subgroup.

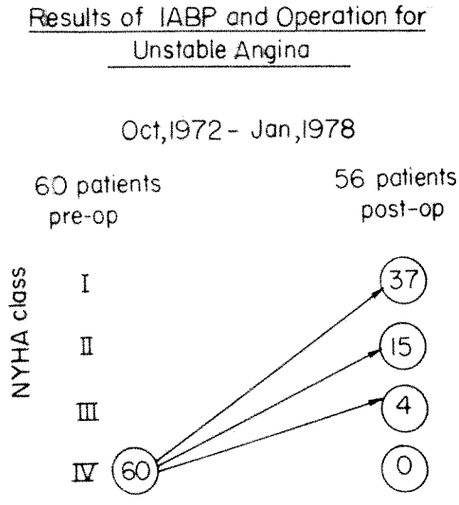


FIGURE 2. Results of intraaortic balloon pumping and operation for medically refractory unstable angina in 60 patients. NYHA class = New York Heart Association functional classification.

Medical versus surgical therapy: The choice of medical versus surgical therapy for unstable angina has received considerable attention from both the medical and the lay press. In a randomized study of 19 medical and 21 surgical patients, Selden et al.[7] found no differences in infarction or mortality 4 months after initiation of treatment. However, the surgically treated patients had a significantly greater functional capacity. In a national cooperative randomized unstable angina study, Russell et al.[8] found no differences in mortality between medically and surgically treated patients at 24 months mean follow-up. In a recent review, Hultgren[1] reported similar findings. Bertolasi et al.,[9] like Selden et al., found no differences in mortality between medical and surgical groups followed to 4 months, but noted a strikingly decreased mortality in the surgical group when the comparison was carried out to 12 months. However, their randomized study can be criticized, because the maximal propranolol dosage in the medically treated patients was only 100 mg/day.

A recent study of nonrandomized patients by Hultgren et al.[13] suggests that bias may enter into the decision to randomize individual patients and that randomized studies to date may not contain a population group representative of all patients with unstable angina. Their report shows a considerable survival advantage for patients treated surgically and suggests that, despite a more uniform definition, we may still be

dealing with an inhomogeneous population. It is obvious from the foregoing that a final judgment concerning the relative efficacy of surgical and medical treatment of unstable angina is premature at this time. For those patients not responding favorably to beta adrenergic blockade, or in whom propranolol is contraindicated, emergency coronary angiography and coronary revascularization may properly be considered despite past evidence that patients with acute ischemia do not tolerate cardiac surgery as well as those operated on electively.[14–18]

Role of intraaortic balloon pumping: The greater operative mortality of myocardial revascularization in patients with preinfarction angina compared with patients with chronic stable angina prompted Gold et al.[4] and Weintraub et al.[2] to use the intraaortic balloon pump in the former group. The physiologic rationale supporting the use of counterpulsation in preinfarction angina has been presented by several groups.[4,19–21] Furthermore, a review of our own clinical material showed that a significant proportion of these patients were suffering from an acute myocardial infarction, which was not always suspected before operation. Similar findings have been confirmed with radionuclide imaging.[22] The reported higher mortality attending bypass operations on patients with recent acute myocardial injury[23] has reinforced our tendency to use counterpulsation. Using balloon support, we were able to revascularize the myocardium of all patients having medically refractory unstable angina; the mortality rate was less than 2 percent, a rate similar to that of elective revascularization of patients with stable angina. Reduced operative mortality has also been reported by others.[5,24,25]

Therapeutic implications: Our experience over the past 7 years with patients having unstable angina has led to certain conclusions and a consequent standardized approach. First, we believe that the institution of early and vigorous medical therapy rarely results in major infarction or death. We currently treat patients with unstable angina with admission to the coronary care unit and an aggressive use of both nitrates and beta adrenergic blockade with propranolol. For those patients whose condition stabilizes with medical therapy, we recommend cardiac catheterization before discharge from the hospital because more than a third of such patients can be expected to be treated surgically in the ensuing months,[8] and because an unusually large proportion of such patients (12 to 15 percent) have left main coronary artery disease. The presence of the latter mandates fairly urgent coronary bypass surgery.[26] Second, we find that there is a subgroup of patients who continue to have unstable angina despite thorough and aggressive medical management. A significant proportion of these patients may either have occult acute myocardial injury or angina consequent upon a recognized acute myocardial infarction. Our data suggest that with modern anesthetic and surgical techniques and with use of the intraaortic balloon pump, such patients can be operated on with a mortality rate approaching that for chronic stable angina. Finally, the good clinical results in these patients with respect to survival, symptomatic relief and rehabilitation appear to be maintained for a significant period of time.

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Medically Refractory Unstable Angina Pectoris. II. Hemodynamic and Angiographic Effects of Intraaortic Balloon Counterpulsation

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Of 60 patients receiving intraaortic balloon counterpulsation for angina refractory to maximal medical therapy, a subgroup of 10 patients underwent left ventricular angiography both with and without counterpulsation. Severe stenosis of the left anterior descending coronary artery was present in all 10 patients. Counterpulsation resulted in a significant decrease in systolic and end-diastolic left ventricular pressures and no increase in cardiac index. Left ventricular diastolic and systolic volume, ejection fraction and regional contraction patterns, often abnormal, were unchanged. However, mean normalized systolic ejection rate was improved by the addition of counterpulsation.

It is concluded that intraaortic balloon counterpulsation has relatively little effect on the left ventricular volume of patients with medically refractory angina pectoris. The symptomatic improvement that takes place seems to occur mainly through the effect of counterpulsation on preload and afterload.

Unstable angina pectoris is a common management problem for cardiologists. Although the short-term mortality rate is relatively low, there is a wide variation in reported long-term survival.[1–6] A number of studies[3,5,7,8] have identified a high risk subgroup of patients characterized by previously stable angina pectoris, ischemic electrocardiographic abnormalities accompanying chest discomfort, and persistent angina at rest despite maximal medical therapy. Because of the recognized danger of myocardial infarction or sudden death, these patients have undergone coronary angiography and coronary bypass graft surgery with[9] and without[4,5,10–13] intraaortic balloon counterpulsation. Although the reported results have been good, the role of counterpulsation in the management of unstable angina remains controversial. The present study was designed to examine the rationale for the use of the intraaortic balloon pump in patients with unstable angina pectoris that is refractory to maximal medical therapy.

Material and Methods

Study Patients (Table I)

Between October 1972 and January 1978, 60 patients with medically refractory unstable angina underwent a combination of intraaortic balloon pump counterpulsation, cardiac catheterization and coronary revascularization.[14] Between September 1976 and September 1977, all such patients with medically refractory unstable angina in whom acute infarction had been excluded by enzymatic and electrocardiographic criteria were asked to have a second left ventriculogram as part of their cardiac catheterization. The 10 patients who acceded to this request form the basis of this report.

There were eight men and two women studied, ranging in age from 38 to 66 years (mean 54). All of the patients had multiple risk factors for coronary artery disease including heavy smoking (six patients), hypertension (six patients), diabetes mellitus (two patients), a positive family history of premature coronary

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TABLE I

Clinical Characteristics of Patients

Case no.	Age (yr) & Sex	Hyper-tension	Dia-betes	Smoking History*	Family History†	Lipid Abnor-mality	Onset of Angina‡	Prior MI§	CHF	ECG Changes With Pain	Relief of Angina by IABP
1	66F	+	0	0	0	+	1	None	0	S-T ↓ leads I, aVL, V_1–V_6	None
2	56M	0	+	1.5 × 40	+	+	21	Ant-lat, 5 mo	+	S-T ↑ leads V_2–V_4	Partial
3	42F	+	0	0	+	0	2	None	0	S-T ↑ leads III, aVF T ↓ leads V_1–V_3	Total
4	38M	+	+	1.5 × 25	+	+	13	Ant-sept, 3 mo	0	S-T ↓ leads I, aVL, V_{4-6}	Partial
5	53M	+	0	3 × 30	0	0	3	None	0	T ↑ leads V_1–V_5	None
6	64M	0	0	2 × 50	0	0	2	None	0	T ↓ leads V_4–V_5	Partial
7	57M	+	0	0	+	0	2	None	0	S-T ↑ leads V_1–V_4	Total
8	48M	0	0	1 × 30	+	+	3	Inf, 48 mo	0	T ↓ leads V_2–V_6	Total
9	52M	+	0	0	0	0	26	Inf, 5 mo	0	S-T ↑ leads I, aVL, V_4–V_6	Total
10	60M	0	0	3 × 30	+	+	9	None	0	S-T ↑ leads II, III, aVF	Total

* Packs per day times years of cigarette smoking.
† Parent, sibling, or child with definite coronary disease before age 55.
‡ Onset of angina pectoris in months before current episode.
§ Site of myocardial infarction (MI), time of infarction in months before current episode.
Ant-lat = anterolateral; Ant-sept = anteroseptal; CHF = congestive heart failure; IABP = intraaortic balloon pump; neg = negative; Inf = inferior; Inv = inversion; ↑ = elevation; ↓ = inversion.

artery disease (six patients) and an abnormal serum lipid pattern (six patients). In three patients angina began with an acute infarction occurring 3 to 5 months before the study. Only one of the patients had X-ray or clinical evidence of congestive heart failure at the time of counterpulsation. In general, there was a rapid progression of symptoms. In six of the patients the current episode of angina began, or recurred after a long pain-free interval, within a 3 week period before counterpulsation.

Transient electrocardiographic S-T and T wave changes with pain were required for entrance into the study and thus were present in all patients. Five patients had transient S-T segment elevation with pain.

Coronary Anatomy (Table II)

In all 10 patients the selective coronary arteriograms demonstrated obstructive lesions in multiple locations. All patients exhibited high grade stenosis (75 to 95 percent) of the proximal left anterior descending artery. The right coronary artery was also the site of high grade stenosis in seven patients, and the left circumflex artery was involved in four. Two patients had marked narrowing of the main left coronary artery.

Protocol

Informed consent was obtained from all patients in the study group. They were admitted to the coronary care unit and placed on complete bed rest with continuous electrocardiographic monitoring. Twelve lead electrocardiograms were obtained while the patients were free of chest discomfort and also during attacks of angina pectoris. Serum creatine kinase, creatine kinase-isoenzyme, serum glutamic oxaloacetic transaminase and lactic dehydrogenase levels were determined, and 12 lead electrocardiograms were taken daily. Patients with evidence of acute infarction by any of the aforementioned criteria were excluded from the study.

Progressively increased dosages of propranolol were administered to each patient until relief of angina pectoris occurred or until a further increase was precluded by the development of bradycardia (heart rate less than 55 beats/min), hypotension (systolic blood pressure less than 105 mm Hg) or congestive heart failure. Nitrates were administered in the

TABLE II

Angiographic Findings

Case no.	LCA	LAD	LCX	RCA	LADD	LCXM
1	0	++++	0	++	0	0
2	0	++++	++++	+++++	0	0
3	0	++++	0	+	0	++
4	++++	++++	++++	++	0	+++
5	++++	++++	++++	0	0	0
6	0	++++	0	+	0	0
7	0	++++	0	++++	++++	0
8	0	++++	+++	++++	0	++++
9	0	++++	0	++++	0	0
10	+	++++	0	++++	0	0

0 = normal; + = slight irregularity of vessel wall; ++ = moderate involvement, not hemodynamically significant (<50 percent); +++ = marked involvement, hemodynamically significant (50 to 75 percent); ++++ = severe involvement (75 to <100 percent); +++++ = total obstruction.
LAD = left anterior descending coronary artery; LADD = left anterior descending coronary artery, diagonal branch; LCA = left coronary artery; LCX = left circumflex coronary artery; LCXM = circumflex coronary artery, marginal branch; RCA = right coronary artery.

form of sublingual nitroglycerin, cutaneously applied nitroglycerin ointment or sublingual isosorbide dinitrate, alone or in combination, until the systolic blood pressure was 105 mm Hg or less. If the patient continued to have episodes of angina pectoris accompanied by transient electrocardiographic S-T and T wave changes after 48 hours of maximal medical therapy, an intraaortic balloon (AVCO Medical Products, Everett, Massachusetts) was inserted with the use of local lidocaine anesthesia.

Hemodynamic and Angiographic Measurements

Cardiac catheterization and angiography were performed within 24 hours of the institution of intraaortic balloon counterpulsation. Beta adrenergic blockade was maintained. Nitrate therapy was continued, although the dose was usually withheld if the systemic systolic pressure was less than 100 mm Hg. Left radial arterial pressure was determined with a Statham P23db transducer through an inlying plastic cannula. All patients were given 5,000 units of aqueous heparin intravenously. Right heart catheterization was performed from the right femoral vein using the percutaneous insertion sheath technique. A no. 7F thermodilution catheter was advanced to the pulmonary artery and pulmonary capillary wedge positions. Using a technique previously described from this laboratory,[15] a ventricular angiographic catheter was advanced from the femoral artery to the left ventricle. Four thermodilution cardiac output determinations as well as pressure measurements were obtained from positions in the pulmonary artery, pulmonary arterial wedge, radial artery and left ventricle. Pressures were recorded on an Electronics for Medicine photographic direct writing transcriber.

Counterpulsation was discontinued for 15 minutes while the pressure measurements were monitored, after which the previously described pressure and flow measurements were repeated and values recorded. With the intraaortic balloon pump turned off, biplane left ventricular cineangiography was performed with 45 ml of sodium meglumine diatrizoate (Hypaque R-M, 75 percent) injected at 12 ml/sec. The pressure and flow measurements were repeated immediately after the completion of the first angiogram. After satisfactory measurements had been obtained (between 2 and 3 minutes), counterpulsation was reinstituted and pressures were monitored for a total of 15 minutes. Without changing the position of the patient or the method of injection of the contrast medium, a second biplane left ventricular cineangiogram was taken during counterpulsation, pressures and flows were remeasured and selective coronary arteriography was performed.

Measurements of ventricular volume and ejection fraction were made using the biplane area-length formula of Dodge et al.[16] The left ventricle was divided by a line from the juncture of the aortic and mitral valves to the apex. This line was divided into four equal segments by drawing three perpendicular axes. Systolic shortening of these chords was measured using standard techniques.[17] Left ventricular stroke work index was determined using the planimetrically determined mean systolic left ventricular pressure, the end-diastolic left ventricular pressure and the average stroke index obtained from four thermodilution determinations of cardiac output and heart rate.

Mean normalized circumferential fiber shortening was calculated using techniques previously described.[18] Mean normalized systolic ejection rate was calculated from the biplane cineangiogram using the technique of Peterson et al.[19]

Data organization and paired sample analysis were performed using the PROPHET computer system of the National Institutes of Health.

Results

Hemodynamic Findings (Table III)

Discontinuation of counterpulsation resulted in increased left ventricular end-diastolic pressure and pulmonary arterial systolic and mean pressures without any significant change in heart rate or cardiac index. The cardiac output and left ventricular end-diastolic pressure increased after the initial left ventriculogram taken without counterpulsation (Fig. 1). Changes of the same magnitude occurred after the angiogram taken during counterpulsation.

Left Ventricular Angiographic Findings (Table IV)

A comparison of the angiograms taken with and without counterpulsation demonstrated no significant changes in left ventricular diastolic and systolic volumes or ejection fraction. In seven patients the determination of the average shortening of all left ventricular chords disclosed an increase during counterpulsation. However,

TABLE III

Effect of Counterpulsation on Hemodynamic Variables

Case	Systolic BP		Systolic PA		Mean PA		CI		LVEDP	
no.	Off	On	Off	On	Off	On	Off	On	Off	On
1	142	126	36	32	24	18	2.16	2.22	24	20
2	117	115	42	32	28	16	2.68	2.31	15	10
3	130	125	36	30	28	26	3.02	2.91	28	28
4	135	125	40	30	30	24	3.38	3.07	18	18
5	140	115	22	18	17	12	2.10	2.21	19	9
6	189	160	18	23	13	14	2.76	3.06	17	13
7	145	130	24	24	15	15	2.04	2.32	9	8
8	135	130	22	22	19	15	2.71	2.82	25	22
9	125	125	25	23	16	12	2.43	2.24	14	10
10	120	105	26	24	18	17	2.58	2.66	10	10
Mean	137	126	29.2	25.8	20.8	16.9	2.59	2.58	17.9	14.8
P	0.003		0.042		0.009		NS		0.012	

Off and on refer, respectively, to without and with counterpulsation.

BP = systemic blood pressure (mm Hg); CI = cardiac index (liters/min per m^2); LVEDP = left ventricular end-diastolic pressure (mm Hg); NS = not significant; *P* = probability; PA = pulmonary arterial pressure (mm Hg).

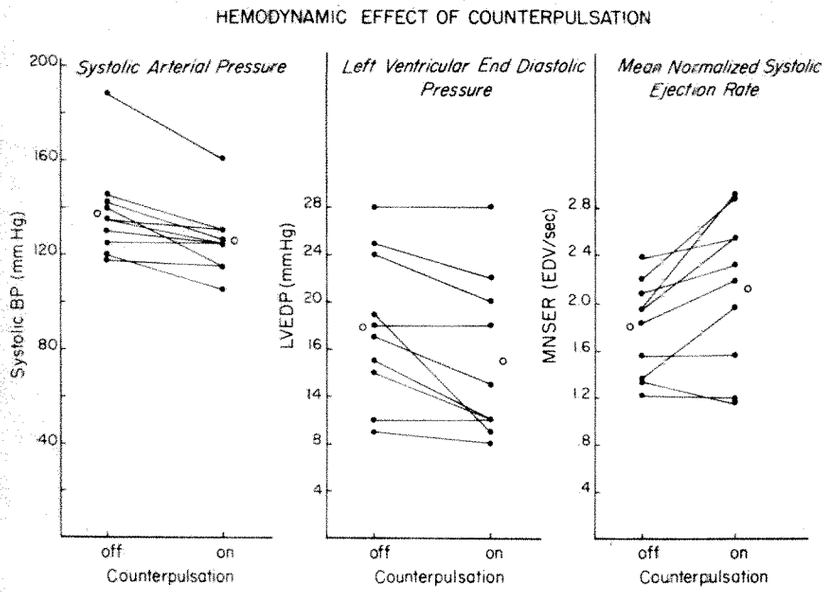


FIGURE 1. Hemodynamic effects of counterpulsation. Individual values are plotted with **closed circles** and the mean values are represented by **open circles.** The decrease in preload and afterload and the improvement in mean normalized systolic ejection rates are statistically significant. BP = blood pressure; LVEDP = left ventricular end-diastolic pressure; MNSER = mean normalized systolic ejection rate.

a marked decrease was observed in two patients, and for the entire group of patients mean chordal shortening was not significantly changed by the addition of intraaortic balloon pumping. Although this result may have been due to two different types of responses to counterpulsation, the number of subjects in the treated group was too small to permit one to make a valid judgment.

Measurements of circumferential fiber shortening and normalized systolic ejection rates were used as an indirect assessment of the contractile state of the myocardium and the effect of counterpulsation on left ventricular contractility. Although circumferential fiber shortening was abnormally low in the control state, and increased to the lower limits of normal with the addition of counterpulsation, this effect was not statistically significant. There was an increase in the mean normalized systolic ejection rate with counterpulsation (Fig. 1).

Discussion

The reported variability in the morbidity and mortality of patients with unstable angina pectoris may be caused by the wide spectrum of population groups reported. The present study was performed on patients fulfilling the most rigid of clinical criteria, that is, (1) chest pain accompanied by transient electrocardiographic changes, (2) angina pectoris persisting despite "maximal" therapy with beta adrenergic blockade and nitrates, and (3) continuation of episodic angina pectoris after 48 hours of hospitalization in an intensive care setting.

Because of the fear that unstable angina might represent a "preinfarction state," there have been a number of clinical trials involving both medical[20] and surgical intervention. Results of early studies showing a marked decrease in mortality with the use of anticoagulation[21–23] were not confirmed by subsequent trials,[24] and the data suffer from a lack of precise definition as well

TABLE IV

Effect of Counterpulsation on Angiographic Variables

Case	Diastolic Volume Index (ml/m²)		Systolic Volume Index (ml/m²)		Ejection Fraction		Average Chordal Shortening		V_{CF}		MNSER	
no.	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On
1	69	65	38	41	0.45	0.37	0.2767	0.1967	0.84	0.67	1.33	1.15
2	212	178	140	123	0.34	0.31	0.1433	0.1700	0.29	0.53	1.21	1.19
3	57	63	16	18	0.71	0.71	0.4200	0.4700	1.19	0.95	2.38	2.55
4	61	67	21	17	0.66	0.75	0.3650	0.4400	1.41	2.04	2.20	2.88
5	109	95	62	39	0.44	0.59	0.2133	0.2433	0.78	0.99	1.35	1.96
6	129	137	43	48	0.67	0.65	0.3550	0.3517	1.46	1.53	2.08	2.32
7	76	82	28	22	0.63	0.74	0.4133	0.4300	0.81	1.51	1.96	2.55
8	124	119	63	64	0.50	0.47	0.2300	0.1717	0.80	0.29	1.55	1.55
9	88	94	37	36	0.59	0.61	0.2883	0.3167	0.87	1.11	1.83	2.19
10	77	93	29	28	0.63	0.70	0.3267	0.4300	0.87	1.49	1.96	2.90
Mean	100.2	99.3	47.7	43.6	0.562	0.590	0.3030	0.3220	0.932	1.111	1.79	2.12
P	NS		NS		NS		NS		NS		0.0155	

Off and on refer, respectively, to without and with counterpulsation.
MNSER = mean normalized systolic ejection rate (end-diastolic volume/sec); NS = not significant; *P* = probability; V_{CF} = circumferential fiber shortening (circumferences/second).

as an absence of anatomic findings obtained from coronary angiography. The importance of the latter is emphasized by the presence of normal coronary anatomy in approximately 10 to 20 percent of patients with unstable angina pectoris.[8]

More recently, interest has focused on agents that may lower myocardial oxygen requirements by decreasing preload, afterload and ventricular volume and contractility.[25–27] Although good symptomatic control may be achieved in approximately 75 percent of patients with unstable angina by using pharmacologic agents, those patients whose angina is refractory to maximal medical therapy are difficult to manage and may have high morbidity and mortality rates.

Reported Results of Counterpulsation Therapy

The use of counterpulsation has resulted in complete cessation of episodic coronary ischemia in 80 percent of these patients and in a marked diminution of symptoms in another 15 percent.[9,28] Although this symptomatic improvement has been presumed to be the result of both decreased myocardial oxygen consumption and increased coronary blood flow, studies in animals[29] and man[30] have produced variable results. Furthermore, these studies were performed in subjects during cardiogenic shock. Steele et al.[31] and Nichols et al.[32] found that counterpulsation resulted in an increased ejection fraction, whereas Kerber et al.[33] noted no improvement in motion and perfusion of ischemic myocardium during balloon pumping. Some of these conflicting results may be explained by a difference between the clinical and experimental situations. The normal coronary anatomic features of man and dog differ considerably. In addition, the experimental dog model usually has a single acute stenosis whereas man usually has multiple stenoses that have developed gradually. Nevertheless, reduction in ischemia and infarct size with the use of counterpulsation[34] and potentiation of myocardial oxygen conservation by the addition of propranolol[35] have been documented in animal studies and provide further support for the use of counterpulsation in the management of patients with refractory angina.

Effect of Counterpulsation on Ventricular Volume and Ejection Fraction

In our study the improvement in cardiac function associated with the intraaortic balloon pump, as measured by an unchanged cardiac index with a decreased left ventricular end-diastolic pressure, was expected to result in a smaller ventricular volume and an increased ejection fraction. Our angiographic volume determinations failed to disclose such a change, a finding that is in disagreement with radionuclide studies in man. In these studies Steele et al.[31] and Nichols et al.[32] found a decrease in ventricular volume and an increase in ejection fraction during counterpulsation. The difference between these and our findings might be due to continued myocardial beta adrenergic blockade in our patients. Another possible explanation for the absence of significant angiographic volume changes during counterpulsation is the order in which the angiograms were taken. To avoid bias, the counterpulsation ventriculogram was taken second. Although the time period between the two examinations was chosen to be sufficiently long to allow for recovery from the known transitory myocardial effect of roentgenographic contrast agents,[36,37] this depressant effect may last considerably longer in an abnormally functioning myocardium. Experimental data with respect to this question do not exist at this time. It is possible, also, that the techniques utilized in this study are not sufficiently sensitive to identify the changes.

Effect on Myocardial Contractility

We examined three indexes of contractility. Both the ejection fraction and circumferential fiber shortening were unchanged by counterpulsation, but these variables may be invalid as a measure of contractility in the presence of localized disorders of myocardial contraction.[38,39] Mean normalized systolic ejection rate is less affected by regional contraction abnormalities and more representative of left ventricular contractility,[19] although it is sensitive to acute changes in preload and afterload.[40] Mean normalized systolic ejection rate was significantly increased during counterpulsation.

Clinical Implications

The use of counterpulsation in patients with unstable angina undergoing revascularization has been associated with a survival rate approaching that of operations for chronic stable angina.[29,41] In 10 patients studied with cardiac catheterization and left ventriculography, decreases in preload and afterload were documented. Although left ventricular contractility appeared to be improved with use of the balloon, ventricular volumes and ejection fraction were not significantly altered. We conclude that the favorable effects of counterpulsation in this group of patients are largely due to the reduction in preload and afterload.

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Prognostic Value of a Persistently Positive Technetium-99m Stannous Pyrophosphate Myocardial Scintigram After Myocardial Infarction

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Technetium-99m stannous pyrophosphate myocardial scintigrams were obtained in 138 clinically stable patients 32.7 ± 47.3 weeks (range 6 to 260) after acute myocardial infarction. Of the 138 patients, 74 (54 percent) had a persistently positive scintigram. Patients with such a scintigram were more likely to have severe angina pectoris, compensated congestive heart failure, anterior location of acute myocardial infarction, Q waves and S-T segment elevation in the electrocardiograms, cardiomegaly, left ventricular dyssynergy (dyskinesia or global dyssynergy), and an ejection fraction of less than 50 percent. During a follow-up period of 11.6 ± 6.9 months after scintigraphy, 42 percent of the patients with a persistently positive scintigram had either a cardiac death, a nonfatal myocardial infarction, unstable angina pectoris or decompensated congestive heart failure compared with 13 percent of the patients with a negative scintigram ($P < 0.001$). Of the 14 patients with cardiac death, 13 (93 percent) had a persistently positive scintigram. A persistently positive scintigram not only was the best single predictor of cardiac death and combined end points, but also added significantly to the predictive ability of the other clinical variables, including age, location of acute myocardial infarct, clinical status, electrocardiographic findings, and chest X-ray findings. It is concluded that technetium-99m stannous pyrophosphate myocardial scintigraphy has prognostic value in patients after acute myocardial infarction.

Current clinical applications of technetium-99m pyrophosphate myocardial scintigraphy include diagnosis, localization and sizing of acute myocardial infarcts.[1–15] Recent studies[16–19] indicate that technetium-99m pyrophosphate myocardial scintigraphy may also have prognostic value in patients with coronary artery disease. Certain scintigraphic patterns during acute myocardial infarction or unstable angina pectoris have been correlated with an unfavorable prognosis.[16–19] In addition, patients with a persistently positive scintigram after acute myocardial infarction tend to be more symptomatic with severe angina pectoris and congestive heart failure.[20,21] The present investigation was undertaken to assess whether technetium-99m pyrophosphate myocardial scintigraphy would yield prognostic information in 138 patients with a previous myocardial infarction.

Methods

Selection of patients: Between November 1975 and September 1977, a total of 138 patients at the Long Beach Veterans Administration Hospital had an ambulatory outpatient follow-up technetium-99m pyrophosphate myocardial scintigram. The study population included 137 men and 1 woman aged 27 to 82 years (mean ± standard deviation 57.0 ± 8.9 years). The criteria for inclusion in the study were: (1) a documented myocardial infarction 6 or more weeks before

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scintigraphy, (2) clinical stability, and (3) no evidence of active myocardial necrosis at the time of scintigraphy as determined by clinical history, electrocardiography and serum enzyme determinations (creatine kinase, glutamic oxaloacetic transaminase and lactic dehydrogenase). At scintigraphy, none of these patients had pericardial disease, valve calcification, neoplastic invasion of the myocardium or recent high energy cardioversion, all of which have been reported to cause positive scintigrams in the absence of acute myocardial infarction.[22–26]

The study population comprised two subgroups. Subgroup A included 102 patients who had a scintigram during the acute myocardial infarction and at follow-up ambulatory scintigraphy 6 to 37 weeks (mean 18 ± 9.2 weeks) after the infarction. Subgroup B included 36 patients who had only an ambulatory follow-up myocardial scintigram 6 to 260 weeks (mean 78 ± 67.1 weeks) after infarction. For the total population, the mean time from myocardial infarction to follow-up scintigraphy was 32.7 ± 47.3 weeks. Informed consent was obtained from all patients participating in this study.

Myocardial scintigraphy: Follow-up myocardial scintigraphy was performed in the same manner as for patients with acute myocardial infarction. All patients were injected with 20 mCi of technetium-99m stannous pyrophosphate containing less than 0.15 mg of tin. Chromatography, as previously described, was performed before each study.[20,27] In all studies, free technetium was less than 1 percent, and reduced hydrolyzed technetium was less than 5 percent. Two hours after injection of the radionuclide, myocardial imaging was performed in three views: anterior, 45° left anterior oblique and left lateral projections. Myocardial scintigrams were recorded using either a Searle Pho/Gamma HP scintillation camera with a Divcon collimator in the converging mode (68 patients) or a Searle Pho/Gamma V with a high resolution collimator (70 patients). Each view contained 500,000 counts with the Divcon collimator or 400,000 counts with the high resolution collimator with the 20 percent window and the photo peak centered on 140 kev. Serial studies on individual patients were performed with the same camera and collimator.

The myocardial scintigrams were interpreted using our grading system for the intensity of myocardial activity, which was graded from 0 to 3+. Zero activity indicated no activity in the area of the left ventricle. An intensity of 1+ was assigned for activity less than that of the ribs, 2+ for activity equal to or greater than rib activity and 3+ for activity equal to or greater than sternal activity. A scintigram of 2+ or greater activity was considered positive.

Myocardial scintigrams were also graded according to the distribution of activity. Regional uptake was considered when activity could be localized to an anatomic wall of the left ventricle. Diffuse uptake was assigned when anatomic location was indeterminant. Delayed imaging 4 hours after injection was performed in all patients with suspected persistent blood pool activity, as determined by persistent radioactivity in the right heart chambers at 2 hours of imaging. Myocardial scintigrams were interpreted by two independent observers without knowledge of the patient's diagnosis or clinical status. If there was any disagreement, the lower score was assigned. There was complete agreement between the two observers on 92 percent of the myocardial scintigrams interpreted.

At follow-up scintigraphy, a cardiologist who had no knowledge of the results of the myocardial scintigrams evaluated all patients and assigned them a clinical classification according to the functional criteria of the New York Heart Association.[28] Each patient also had a posteroanterior and lateral chest roentgenogram.

Follow-up procedures and evaluation: After follow-up scintigraphy, the patients were followed up in our cardiology clinic for 11.6 ± 6.9 months (range 1 to 24). During the follow-up period, 30 of the 138 patients (22 percent) underwent complete right and left heart catheterization and coronary angiography because of angina pectoris. Significant coronary stenosis was defined as 75 percent or greater luminal diameter narrowing of a coronary artery. Left ventricular angiograms were performed in the 30° right anterior oblique projection. Left ventricular end-systolic and end-diastolic volumes were calculated according to the method of Dodge et al.,[29] and a left ventricular ejection fraction was calculated for each patient.

Additionally, types of localized left ventricular segmental contraction abnormalities (dyssynergy) were assessed. Hypokinesia was defined as decreased systolic wall motion, akinesia as absence of systolic wall motion, dyskinesia as paradoxical outward systolic expansion (ventricular aneurysm) and global dyssynergy as severe diffuse impairment of systolic contraction involving both the anterior and inferior walls of the left ventricle. In addition to their initial ambulatory outpatient myocardial scintigram, 17 of the 138 patients (13 percent) had a repeat scintigram during the follow-up period.

Follow-up end points included cardiac death, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, or decompensated congestive heart failure. Cardiac death was further classified as sudden death (death within 6 hours after the onset of symptoms without evidence of myocardial infarction), death from recurrent myocardial infarction with pump failure and death from intractable congestive heart failure. Follow-up data of cardiac deaths were obtained by telephone interviews with the patients' relatives, review of hospital records and results of autopsy examination. All sudden deaths were witnessed. The diagnosis of nonfatal myocardial infarction was based on all of the following: typical history, electrocardiographic changes and classic enzyme alterations. The diagnosis of unstable angina pectoris required the occurrence of angina at rest, lasting no longer than 1 hour and associated with transient ST-T wave changes. Decompensated congestive heart failure was defined as heart failure at rest, confirmed by physical examination and roentgenology, and requiring hospitalization.

Analysis of data: The data are presented as means ±1 standard deviation. Chi square, linear correlations and stepwise multiple regression analysis were utilized to evaluate the significance of the data.[30]

Results

Scintigraphic findings at follow-up scintigraphy (Table I): Fifty-four percent of the 138 patients had a positive myocardial scintigram 6 to 260 weeks (mean 32.7 ± 47.3) after

TABLE I

Characteristics of Follow-up Technetium-99m Pyrophosphate Myocardial Scintigrams

Subgroup	Patients (no.)	Positive Scintigrams				Negative Scintigrams	
		R_3	R_2	D_3	D_2	D_1	0
A	102	2	24	2	25	27	22
B	36	1	9	0	11	10	5
Total	138	3	33	2	36	37	27

D_1, D_2, D_3 = diffuse 1+, 2+ and 3+ activity, respectively; R_2, R_3 = regional 2+ and 3+ activity, respectively; 0 = no activity.

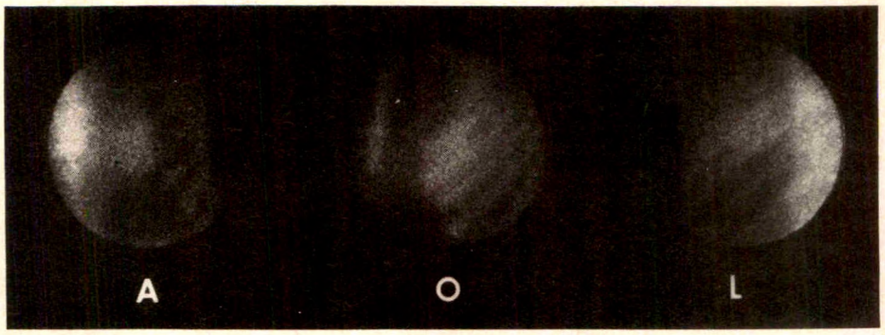


FIGURE 1. Patient 7 (Table V). A persistently positive myocardial scintigram with a regional 2+ abnormality; obtained 35 weeks after an acute subendocardial infarction. Sixty-eight weeks after scintigraphy the patient died suddenly. A = anterior, L = left lateral and O = 45° left anterior oblique projections.

the acute myocardial infarction. There was no significant difference in the incidence of positive scintigrams between patients in subgroup A (52 percent) and subgroup B (58 percent).

Table I indicates the characteristics of the technetium-99m pyrophosphate myocardial scintigrams obtained at follow-up scintigraphy. Of the 74 positive scintigrams, 36 (49 percent) had a regional distribution pattern, 38 (51 percent) had a diffuse distribution pattern and 5 (7 percent) had 3+ intensity of activity. Figure 1 shows a persistently positive scintigram with a regional pattern of abnormality and Figure 2 a persistently positive scintigram with a diffuse pattern of abnormality.

Clinical and myocardial findings at follow-up scintigraphy (Table II): At follow-up scintigraphy, symptomatic patients were more likely than asymptomatic patients to have a positive myocardial scintigram. Seventy of the 110 symptomatic patients (64 percent) with either angina pectoris or compensated congestive heart failure had a positive scintigram compared with 4 of 28 asymptomatic patients (14 percent) (P <0.001). Thirty-four of the 48 patients (71 percent) with a prior anterior wall infarction had a positive scintigram

TABLE II

Clinical and Myocardial Scintigraphic Findings at Follow-up Scintigraphy

	All Patients (total = 138)	Positive Scan (total = 74)	Negative Scan (total = 64)
Mean age (yr)	57.0 ± 8.9	57.4 ± 8.5	56.6 ± 8.9
Weeks from AMI to follow-up scintigraphy	32.7 ± 47.3	35.7 ± 50.1	30.1 ± 45.6
6 to 56	121 (88%)	64 (86%)	57 (89%)
57 to 107	8 (6%)	5 (7%)	3 (5%)
108 to 158	3 (2%)	2 (3%)	1 (2%)
159 to 209	4 (3%)	2 (3%)	2 (2%)
210 to 260	2 (1%)	1 (1%)	1 (2%)
Site of AMI			
Anterior wall	48 (35%)	34 (46%)†	14 (22%)
Inferior wall	54 (39%)	21 (28%)	33 (52%)
Posterior wall	6 (4%)	3 (4%)	3 (5%)
Lateral wall	1 (1%)	0 (0%)	1 (1%)
Subendocardial	29 (21%)	16 (22%)	13 (20%)
History of multiple infarctions	48 (35%)	31 (42%)	17 (27%)
Prior coronary bypass graft surgery	9 (7%)	5 (7%)	4 (6%)
Clinical status at follow-up scintigraphy			
Asymptomatic	28 (20%)	4 (5%)	24 (37%)
Symptomatic	110 (80%)	70 (95%)*	40 (63%)
Angina functional class II	53 (38%)	30 (40%)	23 (36%)
Angina functional class III	20 (15%)	14 (19%)	6 (9%)
Compensated CHF	16 (12%)	13 (18%)	3 (5%)
Compensated CHF and angina	21 (15%)	13 (18%)	8 (13%)
ECG at follow-up scintigraphy			
Normal	4 (3%)	2 (3%)	2 (3%)
Q waves	103 (75%)	61 (82%)§	42 (66%)
LVH	11 (8%)	7 (9%)	4 (6%)
LBBB	3 (2%)	2 (3%)	1 (2%)
Ischemic ST-T wave changes	23 (17%)	13 (18%)	10 (16%)
Nonspecific ST-T wave changes	23 (17%)	10 (14%)	13 (20%)
S- segment elevation	45 (33%)	35 (47%)*	10 (16%)
Atrial fibrillation	1 (1%)	1 (1%)	0 (0%)
VPCs	8 (6%)	3 (4%)	5 (8%)
Cardiomegaly on chest X-ray examination	40 (29%)	28 (38%)‡	12 (19%)

* Probability (P) <0.001 compared with asymptomatic patients or compared with a negative scan.
† P <0.01 compared with inferior wall infarction.
‡ P <0.02 compared with a negative scan.
§ P <0.05 compared with a negative scan.
AMI = acute myocardial infarction; CHF = congestive heart failure; ECG = electrocardiogram; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; VPCs = ventricular premature complexes.

compared with 21 of 54 patients (39 percent) with a prior inferior wall infarction (P <0.01). Of the electrocardiographic features, only the presence of pathologic Q waves or S-T segment elevation correlated significantly with persistent positivity of the myocardial scintigram. Patients with cardiomegaly on chest X-ray examination were more likely than patients with a normal heart size to have a positive myocardial scintigram.

Cardiac catheterization findings correlated with follow-up scintigraphy (Table III): Patients with severe left ventricular segmental contraction abnormalities (dyskinesia or global dyssynergy) and an ejection fraction of less than 50 percent were more likely than patients without these abnormalities to have a persistently positive myocardial scintigram (P <0.05).

Late follow-up cardiac events after scintigraphy (Tables IV to VIII): During the follow-up period of 11.6 ± 6.9 months (range 1 to 24), 14 patients (10 percent) had a cardiac death, 13 patients (9 percent) had a nonfatal myocardial infarction and 12 other patients (9 percent) were hospitalized for unstable angina pectoris or decompensated congestive heart failure. Patients with a persistently positive scintigram had an increased incidence of cardiac death, nonfatal myocardial infarction, unstable angina pectoris and decompensated congestive heart failure.

Tables V and VI summarize the clinical features and scintigraphic findings of the 39 patients who had cardiac death, nonfatal myocardial infarction, unstable angina pectoris or decompensated congestive heart failure during the follow-up period. Figures 1 and 2 illustrate myocardial scintigrams from two of these patients.

The patients' symptom status at follow-up scintigraphy also was a significant predictor of the combined incidence of cardiac death, nonfatal myocardial infarction, unstable angina pectoris and decompensated congestive heart failure. Of the 39 patients who had one of these cardiac end points, 36 (92 percent) had angina pectoris or compensated congestive heart failure, or both, at follow-up scintigraphy; only 3 of 28 asymptomatic patients (11 percent) had these findings (P <0.05). Furthermore, of the 40 symptomatic patients with a negative scintigram, 7 (18 percent) had a cardiac event compared with 29 of 70 symptomatic patients (41 percent) with a positive scintigram (P <0.02).

Positive scintigram as an independent predictor of prognosis: One important question raised by these data was whether a positive scintigram after acute myocardial infarction had independent prognostic value. Indeed, was the scintigram any more useful than simply determining the patient's age and symptom status and obtaining a chest X-ray film and an electrocardiogram? The independence of a predictor variable can be interpreted in two ways: (1) a simple correlation (how its correlation with the criteria compares with the correlations of the other predictor variables with the criteria), and (2) its additive predictive ability (the amount of variance added by the predictor to the variance accounted for by the other predictor variables).

Table VII shows the simple correlation of the clinical variables in Table II thought to be of possible prognostic value and the results of scintigraphy with the cardiac end points of cardiac death, nonfatal myocardial infarction, unstable angina pectoris and decompensated congestive heart failure. As an indicator of cardiac death, a positive scintigram was the best single predictor, followed by cardiomegaly on chest X-ray examination, left ventricular hypertrophy, compensated congestive heart failure and anterior wall myocardial infarction. Inferior wall myocardial infarction was negatively correlated with cardiac death.

For nonfatal myocardial infarction, S-T-segment elevation in the electrocardiogram was the best single predictor, followed by anterior wall myocardial infarction. For unstable angina pectoris, the best single predictor was compensated congestive heart failure, followed by nonspecific ST-T wave changes. Cardiomegaly on chest X-ray examination was negatively correlated with unstable angina pectoris. For decompensated congestive heart failure, cardiomegaly on chest X-ray examination was the best single predictor, followed by compensated congestive heart failure, left ventricular hypertrophy and posterior wall infarction. Angina pectoris and inferior wall myocardial infarction were negatively correlated with decompensated congestive heart failure.

For all cardiac end points, a positive scintigram was the best single predictor, followed by anterior wall myocardial infarction, cardiomegaly on chest X-ray examination, left ventricular hypertrophy, S-T segment elevation and compensated congestive heart failure. Inferior wall myocardial infarction was negatively correlated with all cardiac end points.

Table VIII shows the additive predictive ability of the scintigram over the 18 clinical variables in predicting cardiac death, nonfatal myocardial infarction, unstable angina pectoris and decompensated congestive heart failure obtained by stepwise multiple regression analysis. In multiple regression analysis, the amount of variance in the end point variables accounted for by the predictor variables is calculated by taking 100 times the multiple correlation coefficient (multiple R^2). In Table VIII, column 2 shows the multiple R^2 using the 18 clinical variables excluding the scintigram. Column 3 shows the multiple R^2 when the scintigram is added to these 18 variables. Column 4 shows the change in multiple R^2 added by the scintigram, and column 5 indicates the F value and probability level of this change in multiple R^2.

For cardiac death, the 18 variables excluding the scintigram accounted for 16.6 percent of the variance associated with cardiac death. When the scintigram is added, 21.3 percent of the variance is accounted for, which means that an additional 4.7 percent of the variance was contributed to by the scintigram. The F value for this additive variance was 7.01, which was significant at the P <0.01 level. Similarly, for all cardiac

TABLE III

Cardiac Catheterization Findings Correlated With Follow-up Scintigrams

	Patients (no.)	Positive scan no.	Positive scan %
All patients	30	18	60
Coronary angiography			
1 vessel disease	2	0	0
2 vessel disease	8	6	75
3 vessel disease	20	12	60
Left ventriculography			
Normal contraction	5	3	60
Dyssynergy	25	15	60
Hypokinesia	13	5	38
Akinesia	2	1	50
Dyskinesia	6	6	100
Global dyssynergy	4	3	75
Dyskinesia + global dyssynergy	10	9	90*
Ejection fraction (%)			
>50	16	6	38
<50	14	12	86*
30–50	10	8	80
<30	4	4	100

* Probability (P) <0.05 compared with normal contraction, hypokinesia or akinesia or compared with an ejection fraction of more than 50 percent.

TABLE IV

Incidence of Subsequent Cardiac Events Correlated With Follow-up Scintigrams

	Number of Patients (total = 138)		Positive Follow-up Scans (total = 74)		Negative Follow-up Scans (total = 64)	
	no.	%	no.	%	no.	%
Cardiac death	14	10	13	18†	1	2
Nonfatal myocardial infarction	13	9	9	12	4	6
Decompensated congestive heart failure	5	4	4	5	1	2
Unstable angina pectoris	7	5	5	7	2	3
All cardiac events	39	28	31	42*	8	13

* Probability (P) <0.001.
† P <0.01.

end points, the scintigram contributed an additional 5.3 percent of the variance, with an F value of 8.58 (P <0.005). Thus, for cardiac death and all cardiac end points, the scintigram not only was the best single predictor, but also added to the predictive ability of the other variables, including age, clinical status, location of prior myocardial infarct, electrocardiogram and chest X-ray findings.

Coronary surgery and recurrent myocardial infarction: During the follow-up period, five patients had coronary bypass surgery with no deaths or myocardial infarctions. Two of these patients had a persistently positive scintigram. Repeat scintigraphy after follow-up scintigraphy was performed in 17 patients. Only 1 of the 13 patients with a positive follow-up scintigram had a negative repeat scintigram. This occurred after coronary bypass graft surgery (Fig. 3). All three patients with recurrent myocardial infarction had an increase in the area or intensity of the scintigraphic abnormality.

Autopsy data were available for four patients, all of whom had a prior persistently positive scintigram. One patient had a large ventricular aneurysm, and the other three patients had old ventricular scars.

Discussion

After an acute myocardial infarction patients at high risk for morbidity and mortality include those with advanced age and those who smoke cigarettes or have hypertension, cardiomegaly, congestive heart failure, electrocardiographic abnormalities in the resting 12 lead electrocardiogram, premature ventricular complexes in the resting electrocardiogram, complex or frequent premature ventricular complexes during Holter monitoring or treadmill stress testing, an abnormal treadmill stress test, multivessel coronary artery disease or left

TABLE V

Clinical Features of Patients With Cardiac Death and Scintigraphic Findings

Case no.	Age (yr)	Cause of Death	Time of Follow-up Scintigram After AMI (wk)	Clinical Status at Follow-up Scintigraphy	ECG	Chest X-ray Film	Follow-up Scintigram	Time of Cardiac Death After Follow-up Scintigram (wk)
1	64	SD	25	CHF and angina	Old lateral MI, LVH	Cardiomegaly	Positive, D_2	43
2	53	SD	6	Angina	Old inferior MI, ischemic ST-T wave changes	Normal	Positive, D_2	47
3	68	SD	16	CHF	Old anterior and inferior MI, S-T segment elevation	Cardiomegaly	Negative, 0	51
4	66	SD	108	Angina	Old inferior MI	Normal	Positive, R_2	11
5	51	SD	14	Angina	Old anterior and inferior MI, ischemic ST-T wave changes	Normal	Positive, D_2	23
6	48	SD	84	Angina	Old inferior MI, ischemic ST-T wave changes	Normal	Positive, R_2	50
7	65	SD	35	CHF	LVH, ischemic ST-T wave changes	Cardiomegaly	Positive, R_2	68
8	63	AMI	7	Asymptomatic	Old anterior and inferior MI	Normal	Positive, D_2	46
9	56	AMI	6	Angina	Old anterior MI, LVH, S-T segment elevation	Cardiomegaly	Positive, R_2	50
10	82	AMI	192	Angina	Old anterior and inferior MI	Cardiomegaly	Positive, D_2	61
11	63	CHF	104	CHF and angina	Old anterior MI, LVH	Cardiomegaly	Positive, R_2	58
12	43	CHF	6	CHF	Old anterior MI, S-T segment elevation	Cardiomegaly	Positive, D_2	8
13	59	CHF	15	CHF and angina	Old anterior MI	Cardiomegaly	Positive, R_3	29
14	46	CHF	26	CHF	Ischemic ST-T wave changes	Cardiomegaly	Positive, D_2	20

AMI = acute myocardial infarction; CHF = congestive heart failure; D_2 = diffuse 2+ activity; ECG = electrocardiogram; LVH = left ventricular hypertrophy; MI = myocardial infarction; R_2, R_3 = regional 2+ and 3+ activity, respectively; SD = sudden death; 0 = no activity.

TABLE VI

Clinical Features and Scintigraphic Findings of Patients With Nonfatal Myocardial Infarction, Unstable Angina Pectoris or Decompensated Congestive Heart Failure

Case no.	Age (yr)	Cardiac End Point	Time of Follow-up Scintigram After AMI (wk)	Clinical Status at Follow-up Scintigram	ECG	Chest X-ray Film	Follow-up Scintigram	Time of Cardiac End Point After Follow-up Scintigram (wk)
15	52	AMI	8	Asymptomatic	Old inferior MI, ischemic ST-T wave changes	Normal	Negative, D_1	60
16	60	AMI	9	Angina	Old anterior MI, S-T segment elevation, VPC	Normal	Negative, 0	32
17	52	AMI	6	Angina	Old anterior MI, S-T segment elevation, nonspecific ST-T wave changes	Normal	Positive, R_2	2
18	53	AMI	24	CHF and angina	Old anterior MI, S-T segment elevation	Cardiomegaly	Positive, D_2	36
19	54	AMI	20	CHF	Old inferior and posterior MI, S-T segment elevation	Cardiomegaly	Positive, D_2	5
20	50	AMI	8	Angina	Old anterior MI, S-T segment elevation	Normal	Positive, D_2	16
21	51	AMI	7	Angina	Old inferior MI	Normal	Negative, D_1	5
22	59	AMI	13	Angina	Old inferior MI	Normal	Negative, 0	24
23	56	AMI	8	Angina	Old anterior MI, S-T segment elevation	Cardiomegaly	Positive, R_2	29
24	58	AMI	6	Angina	Nonspecific ST-T wave changes	Normal	Positive, D_2	12
25	74	AMI	19	Angina	Old anterior and inferior MI, S-T segment elevation, VPC	Normal	Positive, D_2	58
26	44	AMI	20	CHF and angina	Old anterior MI, S-T segment elevation, LVH	Cardiomegaly	Positive, R_2	28
27	64	AMI	11	Angina	Old anterior MI, S-T segment elevation	Normal	Positive, D_2	25
28	55	UAP	22	Angina	Old inferior MI	Normal	Negative, 0	48
29	57	UAP	6	Asymptomatic	Old inferior and posterior MI, nonspecific ST-T wave changes	Normal	Positive, D_2	20
30	52	UAP	21	Angina	Nonspecific ST-T wave changes	Normal	Negative, 0	22
31	50	UAP	52	CHF and angina	Old anterior MI, S-T segment elevation	Normal	Positive, R_2	16
32	53	UAP	15	Angina	Old anterior MI, S-T segment elevation	Normal	Positive, R_2	10
33	55	UAP	8	Angina	Old inferior MI, S-T segment elevation	Normal	Positive, R_2	12
34	56	UAP	32	Angina	Nonspecific ST-T wave changes	Normal	Positive, R_2	6
35	61	DCHF	13	Angina	Old inferior and posterior MI, ischemic ST-T wave changes	Cardiomegaly	Positive, R_2	17
36	51	DCHF	8	CHF	Old anterior MI, S-T segment elevation	Cardiomegaly	Positive, R_2	12
37	76	DCHF	8	CHF	Old anterior MI, S-T segment elevation, LVH	Cardiomegaly	Positive, R_2	21
38	53	DCHF	27	CHF	Old anterior and inferior MI, S-T segment elevation, LVH	Cardiomegaly	Positive, D_2	47
39	61	DCHF	7	CHF	Old anterior MI	Cardiomegaly	Negative, D_1	70

AMI = acute myocardial infarction; CHF = congestive heart failure; D_1, D_2 = diffuse 1+ and 2+ activity, respectively; DCHF = decompensated congestive heart failure; ECG = electrocardiogram; LVH = left ventricular hypertrophy; MI = myocardial infarction; R_2 = regional 2+ activity; UAP = unstable angina pectoris; 0 = no activity; VPCs = ventricular premature complexes.

ventricular dysfunction.[31–40] The data from our study indicate that patients with a persistently positive technetium-99m pyrophosphate myocardial scintigram 6 to 260 weeks after acute myocardial infarction also have an increased risk of cardiac morbidity and mortality. Forty-two percent of patients with a persistently positive scintigram had either a cardiac death or nonfatal myocardial infarction or were hospitalized for unstable angina pectoris or decompensated congestive heart failure during a follow-up period of 11.6 ± 6.9 months after scintigraphy. Of 14 patients who had a cardiac death during the following period, 13 (93 percent) had a persistently positive scintigram.

Furthermore, our data indicate that many patients (54 percent in this study) will continue to have a positive scintigram after acute myocardial infarction. This high incidence rate of persistently positive scintigrams was probably due to our patient selection. Patients with severe angina pectoris, compensated congestive heart failure, anterior location of acute myocardial infarction, Q waves or S-T segment elevation in the electrocardiogram, cardiomegaly on chest X-ray examination, an abnormal left ventricular ejection fraction, or severe abnormalities of segmental contraction (dyskinesia or global dyssynergy) were more likely to have a positive scintigram. Other investigators[7,21] have reported inci-

TABLE VII

Linear Correlation of Clinical Variables and Scintigram With Cardiac Death, Nonfatal Myocardial Infarction, Unstable Angina Pectoris, Decompensated Congestive Heart Failure and All Cardiac End Points

Variable	Cardiac Death	MI	UAP	DCHF	All End Points
Age	0.086	−0.042	−0.084	0.081	0.023
History of MI	0.057	−0.027	−0.030	0.021	0.015
Site of infarct					
Anterior wall	0.158‖	0.181§	−0.030	−0.017	0.251†
Inferior wall	−0.171§	−0.106	−0.050	−0.155‖	−0.272†
Posterior wall	−0.072	0.053	0.113	0.149‖	0.103
Subendocardial	0.062	−0.105	0.043	−0.005	−0.008
Prior bypass grafting	0.008	0.015	0.073	−0.051	0.030
Angina	−0.079	0.114	0.087	−0.200‡	−0.020
Compensated CHF	0.176§	−0.027	0.165§	0.233†	0.165§
Positive scintigram	0.264†	0.101	0.083	0.103	0.326*
Electrocardiogram					
Q wave	0.014	0.118	−0.029	0.107	0.116
LVH	0.256†	−0.003	−0.068	0.229†	0.231†
LBBB	−0.050	−0.048	−0.034	−0.029	−0.094
Ischemic ST-T wave changes	0.107	−0.011	−0.103	0.017	0.022
Nonspecific ST-T wave changes	−0.086	−0.011	0.162‖	−0.087	−0.022
S-T segment elevation	−0.029	0.252†	0.051	0.113	0.215‡
Atrial fibrillation	−0.029	−0.028	−0.020	−0.017	−0.054
VPCs	−0.083	0.132	−0.057	0.118	0.051
Cardiomegaly on chest X-ray film	0.261†	0.013	−0.148‖	0.303*	0.238†

* Probability (P) <0.001.
† P <0.005.
‡ P <0.01.
§ P <0.025.
‖ P <0.05.
CHF = congestive heart failure; DCHF = decompensated congestive heart failure; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MI = myocardial infarction; UAP = unstable angina pectoris; VPCs = ventricular premature complexes.

dence rates of persistently positive scintigrams after acute myocardial infarction ranging from 9 to 41 percent. The type of patient selection will determine the incidence of persistently positive scintigrams after acute myocardial infarction.

Prognostic value of a positive scintigram: The analysis of data from this study, utilizing simple correlation coefficients and multiple regression analysis, indicate that a persistently positive scintigram not only was the best single predictor of cardiac death and combined cardiac end points, cardiac death, nonfatal myocardial infarction, unstable angina pectoris and decompensated congestive heart failure during the follow-up period, but also added significantly to the predictive ability of the other clinical variables, including age, location of prior myocardial infarction, clinical status, electrocardiographic findings and chest X-ray findings. These analyses satisfied our criteria for demonstrating that a persistently positive myocardial scintigram after acute myocardial infarction has independent prognostic value. Our data also confirm the previously published reports of Buja et al.[21] and Cowley et al.,[41] who have also noted a more fulminant clinical course in patients with a persistently positive scintigram.

Our data do not negate the importance of other known noninvasive predictors of morbidity and mortality after acute myocardial infarction. Cardiomegaly on chest X-ray examination, anterior or posterior location of acute myocardial infarction, compensated congestive heart failure and electrocardiographic findings of left ventricular hypertrophy, S-T segment elevation or nonspecific ST-T wave changes also correlated with the cardiac end points of our study. Furthermore, in 58 percent of the patients with positive scintigrams a cardiac end point did not occur; thus, caution must be used in assessing the prognostic value of the scintigram in each individual patient.

TABLE VIII

Additive Predictive Ability of the Scintigram to the 18 Clinical Variables* Obtained by Stepwise Multiple Regression Analysis

Cardiac End Point	Clinical Variables Multiple R^2	Scintigram Added Multiple R^2	Multiple R^2 Change	F Value
Cardiac death	0.166	0.213	0.047	7.01†
Nonfatal myocardial infarction	0.129	0.130	0.011	0.14
Unstable angina pectoris	0.086	0.093	0.007	0.91
Decompensated congestive heart failure	0.209	0.213	0.004	0.60
All end points	0.210	0.263	0.053	8.58‡

* Eighteen clinical variables: age, history of multiple myocardial infarctions, four myocardial infarct sites (anterior, inferior, posterior and subdendocardial), prior bypass graft surgery, angina or compensated congestive heart failure, eight electrocardiographic findings (Q waves, left ventricular hypertrophy, left bundle branch block, ischemic ST-T wave changes, nonspecific ST-T wave changes, S-T segment elevation, atrial fibrillation, and ventricular premature beats) and cardiomegaly on chest X-ray examination.
† Probability (P) <0.01.
‡ P <0.005.

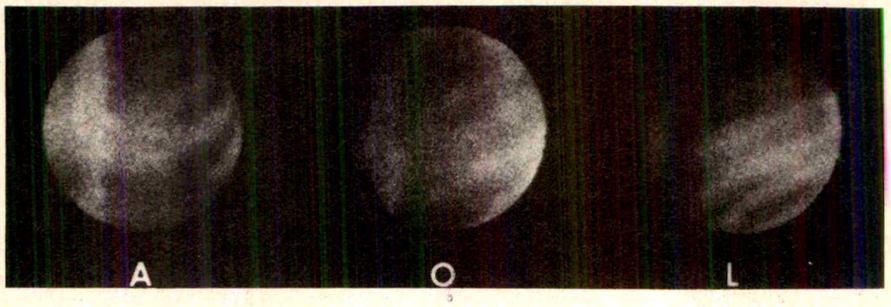


FIGURE 2. Patient 8 (Table V). A persistently positive myocardial scintigram with a diffuse 2+ abnormality, obtained 7 weeks after an acute anterior wall myocardial infarction. Forty-six weeks after scintigraphy, the patient had a new myocardial infarction and died from cardiogenic shock. Abbreviations as in Figure 1.

Intensity and distribution of myocardial activity of a persistently positive scintigram: A persistently positive scintigram after acute myocardial infarction generally shows less activity than that found in acute transmural acute myocardial infarction and approximately the same as that obtained during acute subendocardial infarction.[4,20] At follow-up study, 93 percent of the positive myocardial scintigrams showed 2+ activity, and there was an even distribution of abnormal regional and diffuse patterns. Thus, the scintigraphic diagnosis of recurrent subendocardial infarction in patients with a persistently positive scintigram may be difficult.

Of importance, our study demonstrated the potential ominous nature of a diffusely positive myocardial scintigram after acute myocardial infarction. Of the 14 patients with a cardiac death, 13 (93 percent) had a positive scintigram, and 7 of these 13 patients (54 percent) had a diffusely positive scintigram. Several investigators[42,43] have suggested that a diffusely positive scintigram may be too nonspecific to have clinical value. We believe that a diffusely positive scintigram in patients with coronary artery disease is analogous to nonspecific ST-T wave changes in the electrocardiogram and should be interpreted similarly. Experience from the Coronary Drug Study indicates that even nonspecific ST-T wave changes have an ominous prognostic value after acute myocardial infarction.[34]

Mechanisms for persistently positive scintigram: Proposed mechanisms for a persistently positive scintigram after acute myocardial infarction include persistent blood pool activity, dystrophic calcification of the infarct or associated mural thrombus, ventricular aneurysm or continued cell death in the area of the infarct.[20,21,41,44] Persistent blood pool activity has been attributed to poor binding of the radionuclide, delayed clearance of the radionuclide and abnormal endothelial adherence.[42] Despite careful preparation of the radiopharmaceutical and delayed imaging techniques, persistent blood pool activity may have accounted for some of the positive scintigrams in our study.

For example, some patients with compensated congestive heart failure and cardiomegaly may have had a persistently positive scintigram secondary to persistent blood pool activity due to decreased clearance of the radionuclide caused by decreased cardiac output. Enhancement of even minimal blood pool activity by an enlarged left ventricular cavity with stasis of blood within a large left ventricular aneurysm may also have caused the positive scintigram. However, not all patients with left ventricular dysfunction had a positive scintigram, and the majority of positive scintigrams (65 percent) occurred in patients with normal heart size and left ventricular function.

Dystrophic calcification of the healed infarct or associated mural thrombus or ventricular aneurysm may be a cause of persistently positive scintigrams. Recently Buja et al.[21] postulated that continued cell degeneration (myocytolysis) in a zone of previous infarction may localize technetium-99m pyrophosphate and cause a persistently positive scintigram. Similarly, Cowley et al.[41] found in surgical biopsies of left ventricular scars of patients with a persistently positive scintigram various degrees of degenerating myocardial cells with only mild ultrastructural changes, consisting of homogeneous electron-dense mitrochondrial inclusions. It is thus possible that slow ongoing necrosis in the area of previous infarction may be an important mechanism for a persistently positive scintigram.

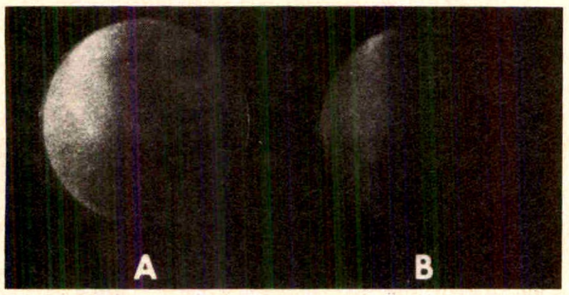


FIGURE 3. Myocardial scintigrams before and after coronary bypass surgery. **A,** preoperative scintigram (2+ abnormality). **B,** a negative scintigram (1+ diffuse abnormality) obtained 6 days postoperatively. This patient had a persistently positive scintigram 30 weeks after an acute subendocardial infarction. Both scintigrams are in the anterior projection.

Duration of positive scintigram: Whether a persistently positive scintigram will remain positive indefinitely is unknown. The incidence of persistently positive scintigrams was not significantly different at the different follow-up periods after acute myocardial infarction (Table II). Positive scintigrams in some patients with unstable or stable angina pectoris have been reported to become negative after coronary bypass graft surgery or aneurysmectomy (Fig. 3).[7–10,45] Further investigation will be required to determine if these pa-

tients will have a more favorable clinical course. However, preliminary data[10] indicate that patients with a positive preoperative myocardial scintigram may also have an increased incidence of surgical mortality.

Scintigraphy during acute phase of infarction as a predictor of prognosis: The majority of our patients selected had the follow-up myocardial scintigram more than 3 months after myocardial infarction. Thus, our study did not address itself to the critical 3 months after acute myocardial infarction, the time interval with the highest mortality rate for patients recovering from acute infarction.[37] Acute infarct scintigraphy may identify these high risk patients for early as well as late cardiac morbidity and mortality. Recent studies[16–18] have defined certain high risk scintigraphic patterns during acute myocardial infarction that have prognostic value. Moreover, preliminary data from this laboratory[20] indicate that patients who continue to have a positive scintigram 14 days after infarction are likely to have a persistently positive scintigram when studied 6 to 37 weeks after the acute infarction. Thus, serial myocardial scintigraphy during acute myocardial infarction may identify patients for both early and late cardiac morbidity and mortality.

Implications: Because of the large incidence of persistently positive scintigrams in patients after acute myocardial infarction, follow-up scintigraphy will be required if one wishes to use this method for the diagnosis of recurrent infarction. Patients with a persistently positive scintigram after acute myocardial infarction have a more fulminant late clinical course with an increased incidence of cardiac death, nonfatal myocardial infarction or hospitalization for congestive heart failure or unstable angina pectoris. Technetium-99m pyrophosphate myocardial scintigraphy has prognostic value in patients after acute myocardial infarction.

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Single Dose Myocardial Perfusion Imaging With Thallium-201: Application in Patients With Nondiagnostic Electrocardiographic Stress Tests

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The role of the single dose technique of myocardial perfusion imaging with thallium-201 in evaluating patients with suspected coronary artery disease was studied in 128 patients undergoing diagnostic coronary arteriography. Significant coronary disease (70 percent or more luminal stenosis) was present in 95 patients. Exercise scans were compared with 4 hour redistribution scans for the presence of new defects with exercise. Myocardial perfusion imaging was significantly more sensitive (85 versus 64 percent, $P < 0.01$) and more accurate (84 versus 71 percent, $P < 0.05$) than stress electrocardiography in detecting coronary disease.

The patients were classified into two groups: group I, 89 patients with diagnostically adequate stress electrocardiograms (that is, positive for ischemia or negative at 85 percent or more predicted maximal heart rate), and group II, 39 patients with nondiagnostic stress electrocardiograms (that is, uninterpretable because of intraventricular conduction disturbance or inadequate because of absence of ischemic S-T depression but failure to achieve 85 percent of predicted maximal heart rate). The sensitivity (87 percent), specificity (85 percent) and accuracy (87 percent) of myocardial perfusion imaging in detecting coronary disease in group I were not significantly different from the results of stress electrocardiography alone (88 percent sensitivity, 85 percent specificity and 88 percent accuracy). In group II scintigraphy was 81 percent sensitive, 69 percent specific and 77 percent accurate in detecting coronary disease; these results were not significantly different from those in group I.

These data indicate that myocardial perfusion imaging with thallium-201 is more sensitive and more accurate than stress electrocardiography in detecting coronary artery disease but offers no advantage for this purpose in patients with diagnostically adequate stress electrocardiograms.

Myocardial perfusion imaging with thallium-201 has been shown to be useful in detecting myocardial infarction[1–5] and in detecting and localizing stress-induced myocardial ischemia due to coronary artery disease.[5–10] Its use in combination with stress electrocardiography improves significantly on the noninvasive diagnosis of coronary artery disease made with stress electrocardiography alone.[5–8]

The scintigraphic demonstration of ischemia requires a comparison of two sets of scans, one performed immediately after exercise and another reflecting the "baseline" state of perfusion. It has recently been shown that a scintiscan performed 4 hours after the exercise scan provides as useful a baseline scan as does a separate resting scan performed on a different day.[5] Thus, the procedure for exercise myocardial perfusion imaging has been made cheaper and simpler by this so-called single dose technique.

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In the present study stress electrocardiography and single dose exercise thallium-201 myocardial perfusion imaging were performed in 128 patients undergoing diagnostic coronary arteriography and ventriculography. The objective of the study was to evaluate the utility of single dose thallium-201 myocardial perfusion imaging in detecting coronary artery disease with respect to the type of electrocardiographic response to stress.

Methods

Patient selection: All patients with known or suspected coronary artery disease undergoing diagnostic coronary arteriography and ventriculography for clinical indications were considered candidates for the study. One hundred twenty-eight consecutive patients who were willing to participate in the protocol were included. Patients with recent myocardial infarction (within 3 months), unstable angina or signs of pulmonary congestion at rest were excluded because of the risks of exercise. Informed written consent was obtained from all patients under a protocol approved by the Institutional Review Board, Health Sciences, Columbia University.

One hundred three patients were men and 25 were women; the mean age was 51.5 years (range 23 to 73). One hundred sixteen patients had a history of chest pain, and 43 had electrocardiographic evidence of prior myocardial infarction. Sixty percent had thallium-201 exercise myocardial perfusion imaging performed within 1 month of coronary arteriography; the longest interval between scintigraphy and arteriography was 1 year. No patients had clinical or electrocardiographic evidence of myocardial infarction or experienced a significant alteration in the pattern of angina between arteriography and scintigraphy. Sixty patients were receiving propranolol and 32 were receiving digitalis at the time of thallium-201 scintigraphy.

Coronary arteriography: Selective coronary arteriography was performed in multiple projections with a modified Judkins technique.[11] A patient was considered to have significant coronary artery disease if one or more major coronary arteries or branches had 70 percent or greater narrowing of luminal diameter. The classification represented a consensus of two observers made without knowledge of the results of thallium-201 scintigraphy.

Of the entire group of 128 patients, 33 (26 percent) had either insignificant coronary artery disease (less than 70 percent stenosis) or normal coronary arteriograms. Ninety-five (74 percent) had coronary artery disease (70 percent or greater stenosis of at least one coronary vessel). Forty patients had single vessel disease, 30 had double vessel disease and 25 had triple vessel disease.

Exercise testing: All exercise tests were performed after an overnight fast. Medications were not altered except that nitrates were omitted on the day of the study. A Teflon® catheter was inserted percutaneously into an antecubital vein and kept patent with an obturator. The skin was carefully prepared and multiple conventional leads (III, aVF, CS_4, CS_5, CS_6) were obtained by positioning limb leads on the torso.[12] The electrocardiogram was monitored continuously and recorded at 1 minute intervals using an Electronics for Medicine DR-8 recorder. Blood pressure was measured with a sphygmomanometer. The exercise test was performed on a treadmill (Quinton Instruments, model 18-54) using a modification of the Bruce protocol.[13] The modification consisted of two preliminary 3 minute stages (1 mile/hour, 0 percent grade and 1 mile/hour, 10 percent grade, respectively) that were used in patients with a history of severely limited exercise capacity.

Exercise was continued until the patient experienced anginal pain, severe fatigue, severe breathlessness, dizziness or light-headedness associated with a reduction in systolic blood pressure of at least 15 mm Hg. All patients performed at least 3 minutes of exercise before the symptom-limited end point was reached. Thallium-201 was injected at this point and the patient was encouraged to continue exercise at the same level for another minute before stopping. No patient had ventricular arrhythmias severe enough to necessitate termination of exercise. The electrocardiogram was monitored for 6 minutes of recovery, and the patient was then taken to the scintillation camera.

Myocardial perfusion imaging: Thallium-201* was administered intravenously as a bolus injection of 1.5 to 2.0 mCi followed by a "flush" injection of 10 cc normal saline solution. Imaging was begun 10 minutes after the injection of tracer during exercise and was repeated 4 hours later for the redistribution scan. The patient was placed in a cradle device, and images were recorded in the anterior and 30° and 60° left anterior oblique views. A multiple crystal scintillation camera computer system (Baird-Atomic, System 77) was used equipped with a 2 inch (5.08 cm) multichannel collimator. Scans were recorded with a 50 to 250 kev window, encompassing the mercury X-rays of thallium-201 (69 to 80 kev) as well as less abundant gamma emissions (135 kev, 168 kev). Exercise images were performed for a preset counting time of 480 seconds in each view, with accumulation of 200,000 to 300,000 counts including approximately 50,000 counts over the heart. Redistribution scintiscans required 640 seconds per view to accumulate similar counts.

The scans were flood-corrected for heterogeneity of crystal efficiency using a uniform thallium-201 liquid pool source. Scans were displayed with 5 point smoothing and a 30 percent background subtraction using a 16 shade color scale.[14] Polaroid® color photographs were used for interpretation.

Interpretation of electrocardiograms: The resting and stress electrocardiograms were interpreted according to criteria of the American Heart Association[15] in a blinded fashion by two cardiologists without knowledge of the angiographic or scintigraphic results. A patient was classified as having an abnormal resting electrocardiogram if (1) there were Q waves indicative of transmural myocardial infarction, (2) there was an intraventricular conduction defect, or (3) there were repolarization (ST-T) abnormalities in two or more leads. The stress electrocardiogram was classified as *positive* for ischemia if the following changes were present for at least three beats with a stable baseline: (1) horizontal or downsloping S-T segment depression of 0.1 mv or more at the J point and lasting at least 80 msec; or (2) S-T segment elevation of 0.1 mv or more in leads without Q waves (S-T segment elevation in leads with pathologic Q waves was not considered an ischemic response). If there was normal repolarization at rest, the S-T segment change was measured from the P-Q junction; if resting repolarization was abnormal, S-T segment depression was measured from the baseline S-T segment level.

A patient who achieved 85 percent of the predicted maximal heart rate[16] without manifesting the S-T segment changes described was classified as having a *negative* stress electrocardiogram. A patient who did not show S-T segment abnormalities but who failed to achieve 85 percent of the predicted maximal heart rate because of fatigue or breathlessness was classified as having an *inadequate* electrocardiographic stress

* Thallium-201 (thallous chloride) was supplied as a sterile pyrogen-free radiopharmaceutical in 0.9 percent saline solution at pH 5–6 in a specific activity of 1 mCi/ml (New England Nuclear or Mallinckrodt, Inc.).

test. A patient who had an intraventricular conduction defect at rest or during exercise was classified as having an *uninterpretable* stress electrocardiogram.

Interpretation of myocardial perfusion images: The myocardial scintiscans were interpreted independently in a blinded fashion by two experienced observers without knowledge of the other clinical data. The rate of interobserver disagreement was 7 percent on the exercise scans and 9 percent on the 4 hour redistribution scans; in these cases the two observers reached a consensus. A scan was classified as normal if there was homogeneous tracer distribution in the left ventricle even if there were small areas of diminished radioactivity (that is, occupying less than 30° of the left ventricular circumference as assessed visually).[17] A scan was said to show a perfusion defect if there was a discrete reduction of tracer activity in an area occupying at least 30° of the left ventricular circumference excluding the aortic and mitral valve planes.

Exercise and redistribution scans were compared for the presence of a new defect with exercise, which was said to occur if a defect was present in an exercise scan but not in the redistribution scan, or if a defect in the redistribution scan was larger in the exercise scan by an area occupying at least 30° of the left ventricular circumference.

Statistical analysis: Analysis of parametric data was performed using Student's *t* test. Group differences in unpaired nonparametric data were analyzed using either a chi square test or Fisher's exact test; group differences in paired nonparametric data were analyzed using McNemar's test.[18]

Results

The patients were classified into two groups on the basis of the type of electrocardiographic response to stress. Group I consisted of 89 patients with a diagnostic stress electrocardiogram (that is, either positive for ischemia or negative for ischemia at 85 percent or more of predicted maximal heart rate). Group II consisted of 39 patients with a nondiagnostic stress electrocardiogram; 7 of these had an uninterpretable and 32 an inadequate electrocardiographic stress test (electrocardiogram negative for ischemia but less than 85 percent of the maximal heart rate was achieved).

The clinical, electrocardiographic and angiographic characteristics of the two groups are summarized in Table I. The two groups did not differ significantly with respect to the incidence or extent of coronary artery disease or with respect to the incidence of Q waves in the resting electrocardiogram. The proportion of patients receiving digitalis was similar in each group; the proportion of patients in group II receiving propranolol (59 percent) was greater than that in group I (42 percent), but the difference was not statistically significant (chi square = 2.64, $P > 0.10$). The mean heart rate achieved during exercise was significantly higher in group I ($P < 0.01$); the incidence of angina during the stress test did not differ significantly in the two groups.

Group I (89 patients with a diagnostic stress electrocardiogram): Table II shows the results of stress electrocardiography and exercise myocardial perfusion imaging with thallium-201. Stress electrocardiography correctly identified 61 of 69 patients with coronary artery disease and 17 of 20 patients with a normal coronary arteriogram. Myocardial perfusion imaging revealed new defects on exercise in 60 of the 69 patients with coronary artery disease; 3 of the 20 patients with a normal coronary arteriogram had a false positive exercise scan. Two patients with coronary artery disease had both a false negative stress electrocardiogram and a false negative exercise scan. The sensitivity, specificity, accuracy and predictive value of the two tests in detecting coronary artery disease were not significantly different. Combining the test results (that is, classifying as a positive result either a positive stress electrocardiogram *or* a new scan defect, and classifying as a negative result the presence of *both* a negative stress electrocardiogram and no new scan defect yielded 97 percent sensitivity but only 70 percent specificity.

TABLE I

Clinical, Electrocardiographic and Angiographic Findings

	Group I (no. = 89)	Group II (no. = 39)
Age (mean and range) (yr)	52.4 (32–73)	49.6 (23–70)
Sex	72M,17F	31M,8F
Drug therapy at time of study		
Propranolol	37 (42%)	23 (59%)
Digitalis	22 (25%)	10 (26%)
Q waves	29 (33%)	14 (36%)
CAD (≥70% stenosis)		
1 vessel	30 (43%)	10 (38%)
2 vessel	22 (32%)	8 (31%)
3 vessel	17 (25%)	8 (31%)
Total	69 (78%)	26 (67%)
Normal	20 (22%)	13 (33%)
Exercise HR*	138 ± 32	121 ± 10
Exercise angina	42 (47%)	18 (46%)

* Probability (P) <0.01.

CAD = coronary artery disease; HR = heart rate (beats/min ± standard deviation); Q waves = significant Q waves in the resting electrocardiogram.

TABLE II

Results of Stress Electrocardiography and Myocardial Perfusion Imaging in Group I (diagnostic stress electrocardiogram)

	CAD (no. = 69)			Normal (no. = 20)	
	Exercise MPI			Exercise MPI	
	+	−		+	−
Stress ECG +	54	7	Stress ECG +	0	3
Stress ECG −	6	2	Stress ECG −	3	14

	Stress ECG	Exercise MPI	Combined
Sensitivity*	88%	87%	97%
Specificity†	85%	85%	70%
Accuracy‡	88%	87%	91%
Predictive Value§	95%	95%	91%

* Sensitivity = TP/(TP + FN).
† Specificity = TN/(TN + FP).
‡ Accuracy = (TP + TN)/(TP + FP + TN + FN).
§ Predictive value (for a positive test result) = TP/(TP + FP).

CAD = coronary artery disease; ECG = electrocardiogram; FN = false negative; FP = false positive; MPI = myocardial perfusion imaging; TN = true negative; TP = true positive; + = an abnormal study; − = a normal study.

The incidence rate of positive stress electrocardiograms in the 69 patients with coronary artery disease in group I was 83 percent in those with single vessel, 91 percent in those with double vessel and 94 percent in those with triple vessel disease. The incidence rate of new scan defects was 80 percent in those with single vessel, 91 percent in those with double vessel and 94 percent in those with triple vessel disease. There was no significant difference between stress scintigraphy and stress electrocardiography with respect to sensitivity of detection by number of diseased vessels.

Group II (39 patients with a nondiagnostic stress electrocardiogram): Figure 1 shows the electrocardiogram and thallium-201 scintiscans in a 30 year old patient with atypical chest pain and a normal resting electrocardiogram. The patient was receiving 80 mg of propranolol daily. During exercise he was able to perform 10.5 minutes of the Bruce protocol, stopping because of chest pain. His maximal heart rate was 144 beats/min, which is 76 percent of the predicted maximum. Stress electrocardiography did not show ischemic S-T segment changes but was interpreted as inadequate (because of failure to reach 85 percent of the predicted maximal heart rate). The thallium-201 scan on exercise showed an inferoapical perfusion defect that was not present 4 hours later. Subsequent coronary arteriography revealed occlusion of the right coronary artery.

Table III lists the results of myocardial perfusion imaging in the 39 patients with a nondiagnostic stress electrocardiogram. Myocardial perfusion imaging correctly classified six of seven patients (86 percent) with an uninterpretable stress electrocardiogram and 24 of 32 patients (75 percent) with an inadequate stress electrocardiogram. The sensitivity, specificity, accuracy and predictive value of exercise myocardial perfusion imaging in detecting coronary artery disease in patients in whom stress electrocardiography was nondiagnostic (group II) were not significantly different from the results obtained in group I.

Twenty-two of the 32 patients with an inadequate electrocardiographic stress test had coronary artery disease; 9 had single vessel, 6 had double vessel and 7 had triple vessel disease. Eighteen of these patients (82 percent) had new scan defects with exercise, and three of the four with a false negative scan had single vessel disease. Of the 10 patients without coronary artery disease, four had a false positive scan; three of these four patients had congestive cardiomyopathy as defined by the criteria of Goodwin.[19]

Role of propranolol: Failure to achieve 85 percent of the predicted maximal heart rate may be influenced by the administration of beta adrenergic blocking agents. Seventeen of the 22 patients (77 percent) with coronary artery disease and an inadequate stress elec-

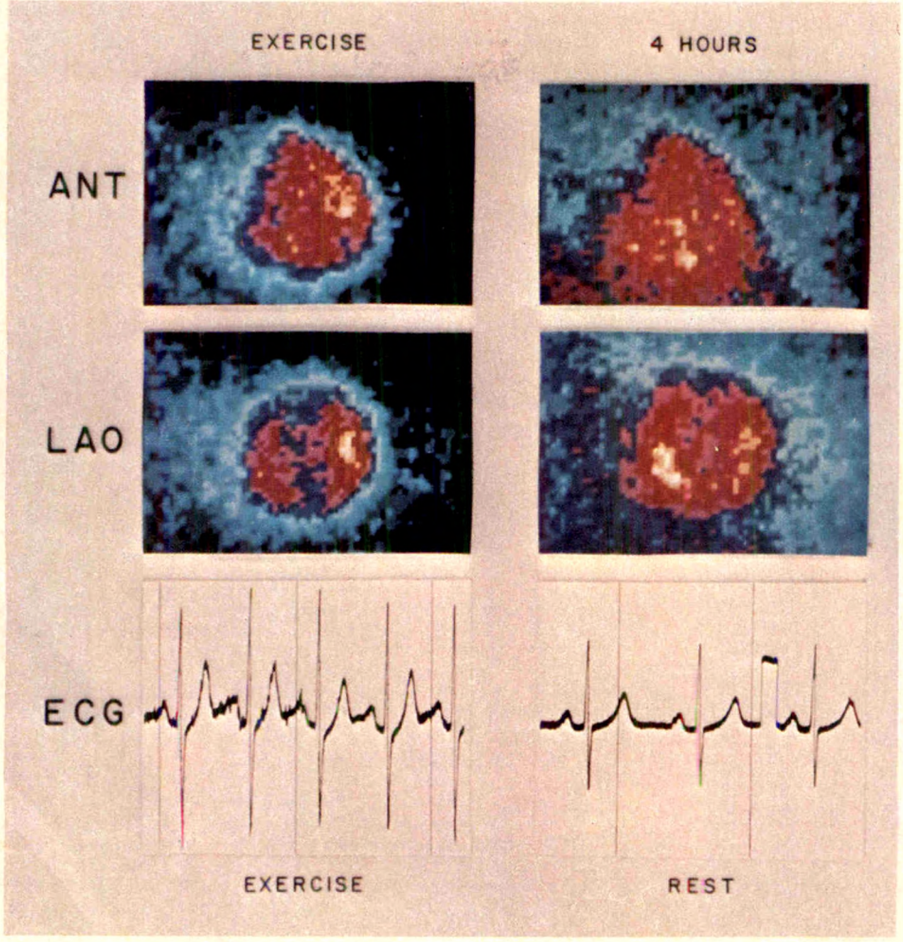


FIGURE 1. Thallium-201 myocardial perfusion scintiscans and electrocardiograms (ECG) in a 30 year old man with atypical chest pain. Illustrated are the scintiscans performed after exercise injection (EXERCISE) and after redistribution (4 HOURS), in the anterior (ANT) and 30° left anterior oblique (LAO) views. Tracer activity is color-coded: yellow, representing the greatest activity, is followed by red, lavender, blue and black (least activity). An inferoapical perfusion defect is evident in the exercise scintiscans; the 4 hour scintiscans are normal. The resting electrocardiogram is normal. During exercise the patient experienced chest pain, but the stress electrocardiogram did not show ischemic S-T segment changes; however, the test was interpreted as inadequate because the patient failed to achieve 85 percent of the predicted maximal heart rate. Coronary arteriography revealed occlusion of the right coronary artery. (Time lines are 1 second apart and the standardization is 1 mv).

trocardiogram in group II were receiving propranolol at the time of study. This proportion was significantly greater than the proportion of patients with coronary artery disease and a diagnostic stress electrocardiogram (group I) who were receiving propranolol (32 of 69, $P < 0.05$). However, the mean heart rate achieved by the 17 patients receiving propranolol who had an inadequate stress electrocardiogram (maximal heart rate achieved 114 ± 16 beats/min [mean ± standard deviation]) was not significantly different from that achieved by the 32 patients receiving propranolol who had a diagnostic stress electrocardiogram (maximal heart rate achieved 111 ± 28 beats/min). Similarly, the incidence rates of angina during exercise (12 of 17 [71 percent] versus 23 of 32 [72 percent]) and of new scan defects (15 of 17 [88 percent] versus 28 of 32 [88 percent]) were not significantly different. Moreover, the incidence of new scan defects in the 37 patients with coronary artery disease and a diagnostic stress electrocardiogram who were *not* receiving propranolol at the time of study (32 of 37 [86 percent]) did not differ significantly from the incidence of new scan defects among patients receiving propranolol.

Results for the entire study group: Figure 2 summarizes the results of stress electrocardiography and myocardial perfusion imaging in the entire group of 128 patients. As in previous reports,[5–8,10] myocardial perfusion imaging was significantly more sensitive than stress electrocardiography (85 versus 64 percent, $P < 0.01$) in detecting coronary artery disease. The observed difference in specificity between the two tests (79 versus 91 percent) was not statistically significant. Myocardial perfusion imaging correctly classified 107 of the 128 patients (84 percent accuracy versus 71 percent accuracy for stress electrocardiography) ($P < 0.05$).

TABLE III

Results of Myocardial Perfusion Imaging in Group II (nondiagnostic stress electrocardiogram)

	CAD (no. = 26)			Normal (no. = 13)	
	Exercise MPI			Exercise MPI	
Stress ECG	+	−	Stress ECG	+	−
Unint.	3	1	Unint.	0	3
Inad.	18	4	Inad.	4	6

	Exercise MPI
Sensitivity	81%
Specificity	69%
Accuracy	77%
Predictive value	84%

CAD = coronary artery disease; Inad. = inadequate stress electrocardiogram; MPI = myocardial perfusion imaging; Unint. = uninterpretable stress electrocardiogram; + = new scan defect; − = no new scan defect.

Discussion

Single versus double dose thallium-201 scintigraphy: Single dose myocardial perfusion imaging with thallium-201 utilizes a scintiscan obtained 4 hours after exercise injection of tracer as the baseline scan for comparison with the exercise scan. The observation of a new defect that is not present in the 4 hour redistribution scan is presumptive evidence of myocardial ischemia due to obstructive coronary artery disease.[5,20] The conventional method of myocardial perfusion imaging with thallium-201 uses a separate thallium scan that is performed at rest on a different day for this comparison.

In this study single dose myocardial perfusion imaging detected coronary artery disease with 85 per-

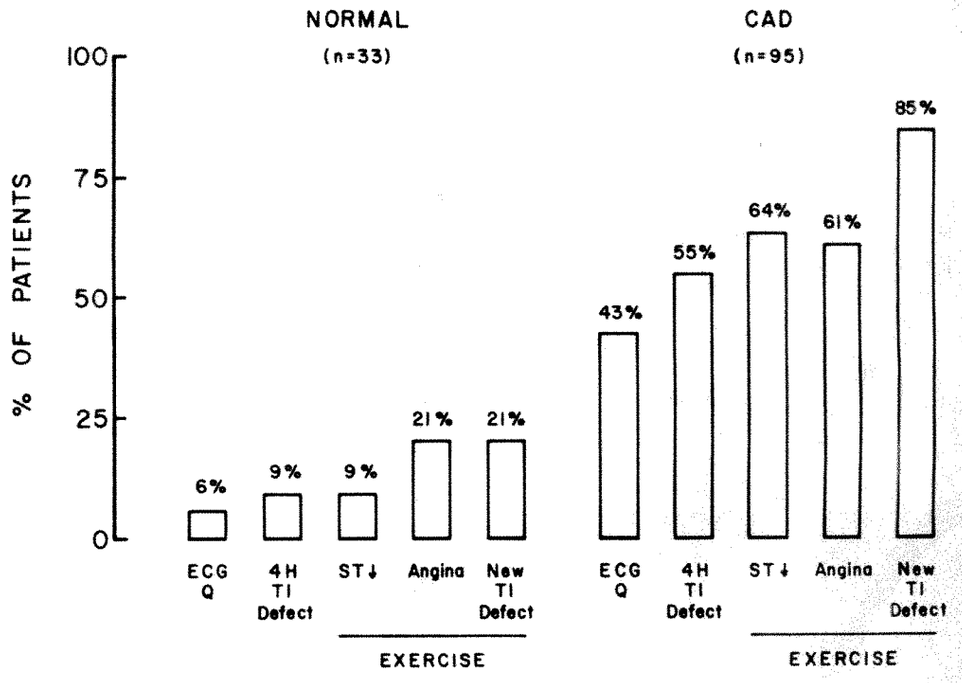


FIGURE 2. Results of thallium-201 (TI) myocardial perfusion imaging and electrocardiography (ECG) in the entire group of 128 patients. In the patients with coronary artery disease (CAD), redistribution (4 H) thallium defects were more common than Q waves (55 versus 43 percent, $P < 0.05$). New thallium defects with exercise were more prevalent than ischemic S-T segment depression (ST↓) (85 versus 64 percent, $P < 0.01$). The results in patients with insignificant (less than 70 percent stenosis) or no coronary disease (NORMAL) reveal 21 percent false positive exercise scans and 9 percent false positive S-T depressions; this difference is not statistically significant.

cent sensitivity, 79 percent specificity and 84 percent accuracy. The sensitivity level is comparable with that previously reported for double dose thallium-201 scintigraphy[6–8] and for studies utilizing only the exercise scan.[9,10] The observed specificity was somewhat lower than that found in other series,[7,9,10] and this difference may be due to the inclusion in our study of five patients with cardiomyopathy and a normal coronary arteriogram; abnormal myocardial blood flow[21] and false positive thallium-201 scans have been reported[22,23] in such patients.

Stress scintigraphy versus stress electrocardiography: In the entire group of 128 patients, myocardial perfusion imaging was significantly more sensitive than stress electrocardiography in detecting coronary artery disease. Previous studies comparing stress electrocardiography with myocardial perfusion imaging also showed that scintigraphy was significantly more sensitive for this purpose.[5–8,10] However, little attention has been paid to the relation between the nature of the electrocardiographic response to stress and the results of thallium-201 scintigraphy.

In our study the levels of sensitivity, specificity and accuracy of myocardial perfusion imaging in detecting coronary artery disease in patients with a diagnostically adequate stress electrocardiogram (group I) were similar to the values with stress electrocardiography alone. Because no previously reported study of exercise scanning with thallium-201 has separated the patients in this manner, direct comparisons are difficult. Botvinick et al.[8] found scintigraphy more sensitive than stress electrocardiography (85 versus 67 percent) in patients with an isoelectric S-T segment at rest. However, they included four patients with coronary artery disease and a negative stress electrocardiogram at suboptimal stress (less than 85 percent of predicted maximal heart rate); in our study such patients were placed in the nondiagnostic group (group II). If these four patients are eliminated, the sensitivity levels of scintigraphy and stress electrocardiography in their series did not differ significantly (83 and 78 percent, respectively). Verani et al.[10] also reported no statistically significant difference between the sensitivity of scintigraphy (77 percent) and exercise electrocardiographic testing (86 percent) in patients with a diagnostic exercise electrocardiogram.

The sensitivity level (88 percent) of the stress electrocardiogram in detecting coronary artery disease in the 89 patients in our group I is higher than that previously reported in other series.[6–9] One explanation for this is our inclusion of patients with resting S-T segment abnormalities who have further S-T depression with exercise; this has been reported to yield increased sensitivity[24] at the expense of decreased specificity (that is, more false positive results).[25] However, when the patients with resting S-T segment depression were separated from those with isoelectric S-T segments at rest, there was no significant difference in sensitivity or specificity between the two groups. Thus the relatively high sensitivity of stress electrocardiography in these patients probably reflects differences in patient population.

Patients with uninterpretable or inadequate electrocardiographic stress tests: The results of thallium-201 myocardial perfusion imaging for detecting coronary artery disease in the 39 patients in group II (81 percent sensitivity and 69 percent specificity) were not significantly different from those in the patients in group I. The rationale for using myocardial scintigraphy in patients with resting or exercise-induced left bundle branch block or intraventricular conduction disturbance is clear: the electrocardiographic changes of ischemia may be undetectable.[26] There is no reason to suspect that the results of scintigraphy in such patients would differ from those in patients with a diagnostic stress electrocardiogram.

Thirty-two of the patients in group II had a negative stress electrocardiogram but failed to reach 85 percent of predicted maximal heart rate, thus raising the question whether the amount of exercise performed was adequate to induce ischemia. McLaughlin et al.[27] studied 12 patients at two levels of exercise, and were able to identify at light exercise only 53 percent of the ischemic thallium-201 defects seen at maximal exercise. In our study none of the 22 patients with coronary artery disease and an inadequate stress electrocardiogram had an ischemic electrocardiographic response, although angina developed in 16 and 18 had a perfusion defect on scanning. This suggests that the mechanism or mechanisms whereby ischemic S-T segment depression occurs in the exercise electrocardiogram[26] are not identical with those that result in angina or an exercise scan defect.

Seventeen of the 22 patients with coronary artery disease and an inadequate stress electrocardiogram were receiving propranolol at the time of study. Previous studies have demonstrated that therapeutic doses of propranolol result in a significant reduction of heart rate for a given exercise work load in normal volunteers[28,29] and in patients with heart disease.[28,30] Thus, many of the patients in group II may have failed to achieve 85 percent of predicted maximal heart rate because of therapeutic beta blockade. However, the mean heart rate achieved by these 17 patients did not differ significantly from that achieved by the patients in group I who were receiving propranolol. Furthermore, the incidence of new scan defects was not significantly different among patients receiving propranolol who had diagnostic or inadequate electrocardiographic stress tests and patients not receiving propranolol who had diagnostic tests. These data suggest that the amount of exercise performed by these 17 patients receiving propranolol was adequate to induce ischemia despite the absence of ischemic S-T segment changes in the stress electrocardiogram.

Previous reports of myocardial perfusion imaging with thallium-201 in patients with nondiagnostic stress electrocardiograms have also demonstrated the usefulness of scintigraphy in this group. Botvinick et al.[8] correctly classified 17 of 19 patients with equivocal

stress electrocardiograms, and Verani et al.[10] correctly identified 24 of 26 patients with nondiagnostic exercise electrocardiogram tests. However, in no previous study have the data suggested that the enhanced sensitivity of thallium-201 myocardial perfusion imaging in detecting coronary artery disease is confined to such patients.

Exercise-induced ischemia could not be detected electrocardiographically in the 26 patients in this study who had coronary artery disease and a nondiagnostic stress electrocardiogram. However, 14 of these patients had Q waves in the resting electrocardiogram, and a presumptive diagnosis of coronary artery disease might have been made on this basis. Yet even in patients with diagnostic Q waves it is often useful to know whether additional coronary disease is present involving vessels other than the one that presumably caused the infarct. Therefore the demonstration of exercise-induced ischemia is most important, and in the 21 patients in group II with new scan defects during exercise it could be shown only with myocardial perfusion imaging.

Implications: Our data show that stress electrocardiography and thallium-201 myocardial perfusion imaging had comparable sensitivity levels for the detection of coronary artery disease in patients whose stress electrocardiogram was diagnostic. The sensitivity of myocardial perfusion imaging in detecting coronary artery disease did not differ significantly in patients with and without a diagnostic stress electrocardiogram. These results imply that for detecting coronary artery disease, the primary utility of myocardial perfusion imaging is in the evaluation of patients with a nondiagnostic stress electrocardiogram.

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CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with oral maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure antinuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be usediconcomitantly with procainamide.

ADVERSE REACTIONS: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported in patients on oral maintenance therapy. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

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The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative antiarrhythmic therapy.

DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide analogue of procaine hydrochloride and is available for oral administration as veneer-coated tablets and capsules providing 250 mg, 375 mg, and 500 mg procainamide hydrochloride.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment c regular atrioventricular conduction, procainami should be stopped and the patient re-evaluatec

In the presence of both liver and kidney dama normal dosage may produce symptoms of over- dosage—principally ventricular tachycardia an severe hypotension.

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ADVERSE REACTIONS: Hypotension is rare w oral administration. Serious disturbances of car rhythm such as ventricular asystole or fibrillatic are more common with I.V. administration.

Large oral doses may sometimes produce an rexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus been reported in patients on oral maintenance therapy (see Precautions). Reactions consistin fever and chills have been reported, including case with nausea, vomiting, abdominal pain, ac hepatomegaly, and a rise in serum glutamic oxa acetic transaminase following single doses of t drug. Agranulocytosis has been occasionally reported following repeated use of the drug, ar deaths have occurred. Therefore, routine bloo counts are advisable during maintenance proc amide therapy; and the patient should be instru to report any soreness of the mouth, throat or g unexplained fever or any symptoms of upper r ratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cel depression, procainamide therapy should be d continued and appropriate treatment should b instituted immediately. Bitter taste, diarrhea, w ness, mental depression, giddiness, psychosis hallucinations, and hypersensitivity reactions as angioneurotic edema and maculopapular ra have been reported.

For full prescribing information, consult pac insert.

HOW SUPPLIED: Pronestyl Tablets (Procainar Hydrochloride Tablets) and Pronestyl Capsule (Procainamide Hydrochloride Capsules USP) vicing 250 mg, 375 mg, and 500 mg procainan hydrochloride are available in bottles of 100 ar Unimatic® single-dose packaging in cartons o The 250 mg and 500 mg tablets and capsules also available in bottles of 1000.

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he unround Offset and Offset Dx ECG monitoring electrode... pecially created to solve problems.

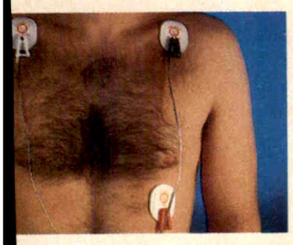
round for secure, estricted electrode cement.
unique elliptical design ffset electrodes permits cement on almost any body and ensures conformation body contours. The special activated adhesive resists tact loss due to perspiration n when used on diaphoretic ents) and loosening action sed by prep solutions.

Unround to reduce motion artifact and ensure base-line stability.
The Medi-Trace® Offset electrode separates the snap from the gel column, connecting them with a silver/silver chloride conductor. The result? Little or no movement of the gel column, producing a superior trace that virtually eliminates motion artifact. Since the snap is over the adhesive, leadwire induced artifact and loose electrodes caused by leadwire tugging are virtually eliminated.

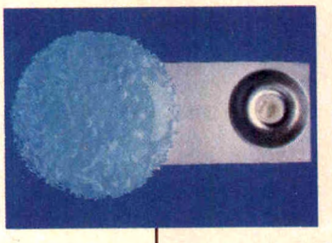
Unround, the result of new technology in ECG monitoring electrodes.*
Advanced technology assures unprecedented conductivity and an end to trace deterioration problems. Specially formulated gel prevents premature dry-out and provides low impedance for a strong, reliable trace. In actual defibrillation tests, Offset electrode trace recovery occurred in less than one second!

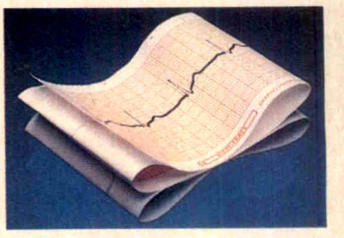
Uninterrupted ECG monitoring is virtually assured.

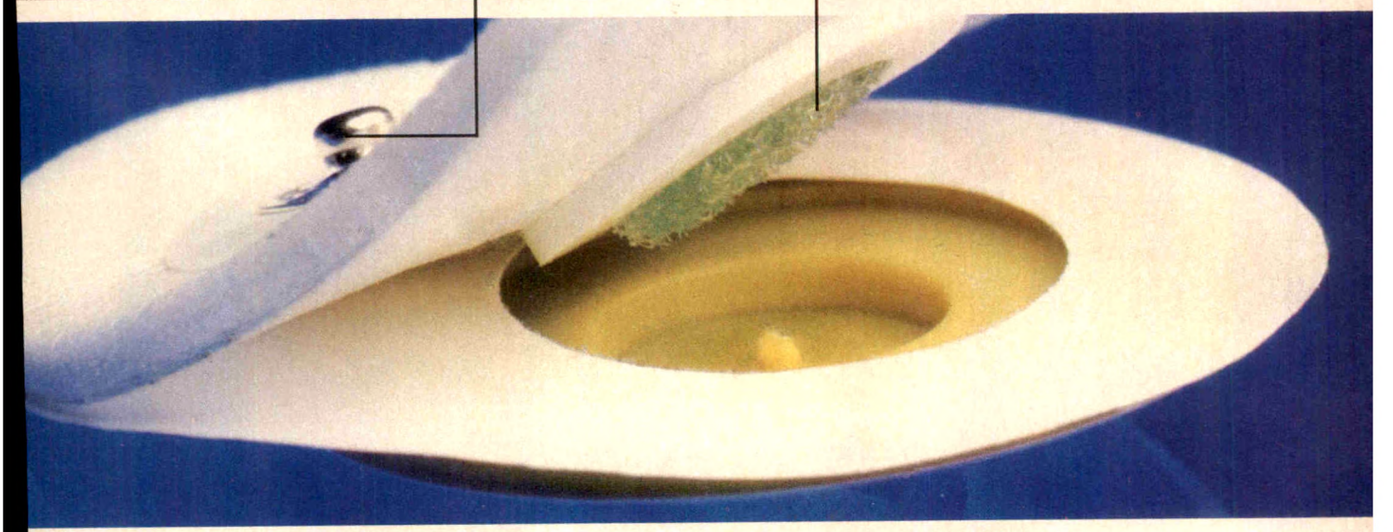
Unround to result in a superior trace.
The soft, flexible gel ring maintains a stable gel column, even during patient and/or leadwire movement. Motion artifact is greatly reduced. Further, the specially formulated low impedance gel ensures base-line stability and minimizes patient skin irritations. The result? A rapid, strong, clear trace that's trouble free.











t Dx... all the benefits fset ECG monitoring rodes... Plus
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"aggressive" adhesive, tant with problem patients rocedures
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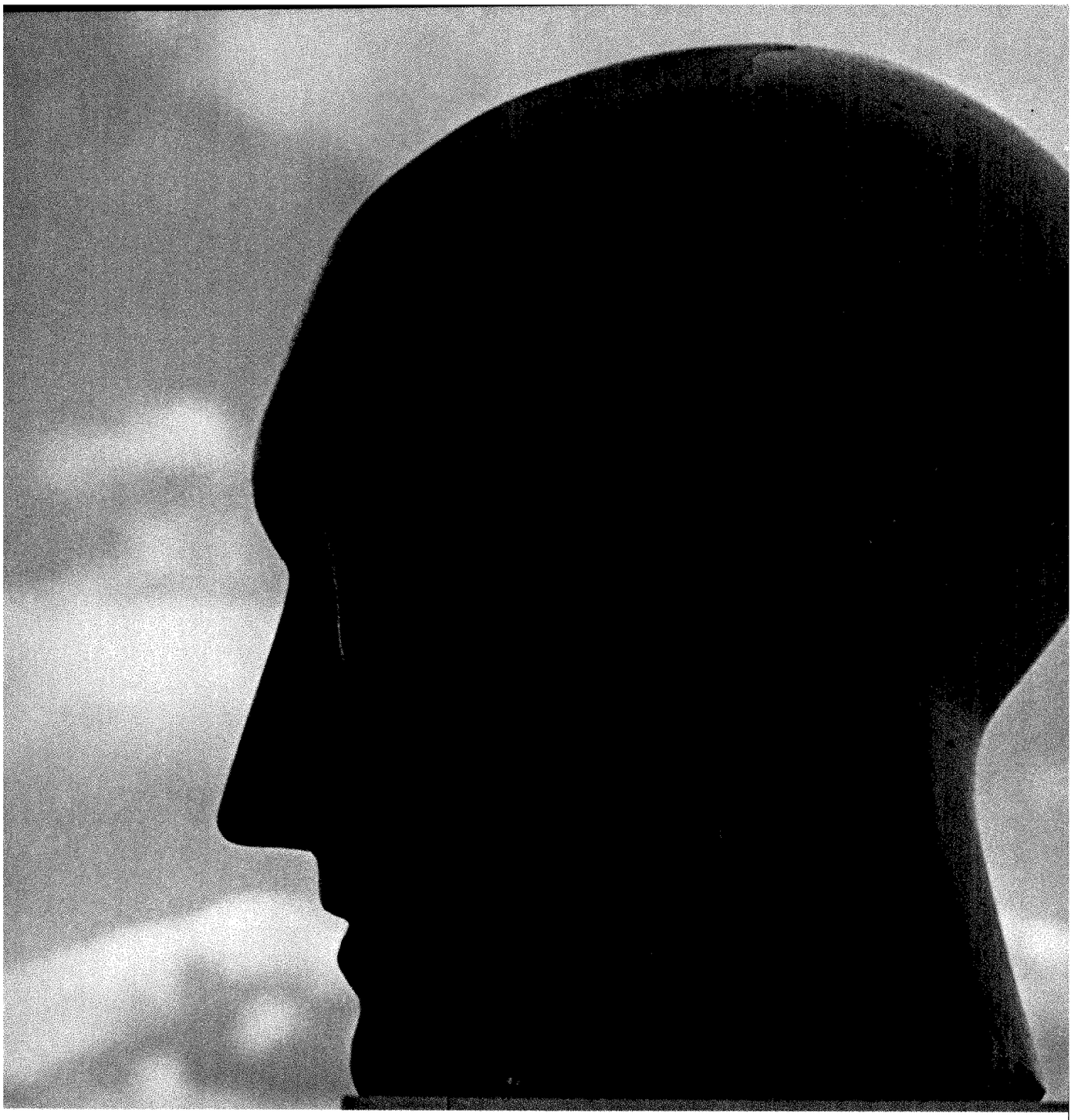
Unround Offset and Offset Dx... part of a total ECG monitoring system.
Packaged for your convenience, Offset electrodes are available in singles, 3's and 25's. Offset Dx electrodes come in singles, 5's and 25's. A multiple layer foil package maintains a clean product that is virtually impervious to moisture/vapor transmission.

Offset and Offset Dx are part of our total ECG monitoring system that includes a complete line of cables, leadwires, recording charts and patient record forms.

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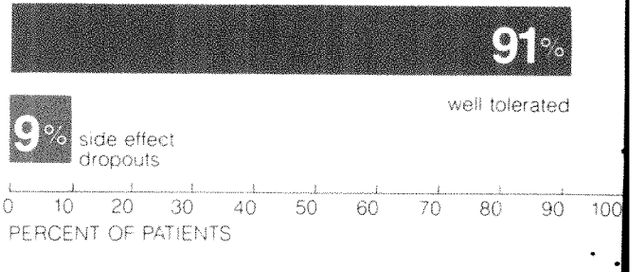
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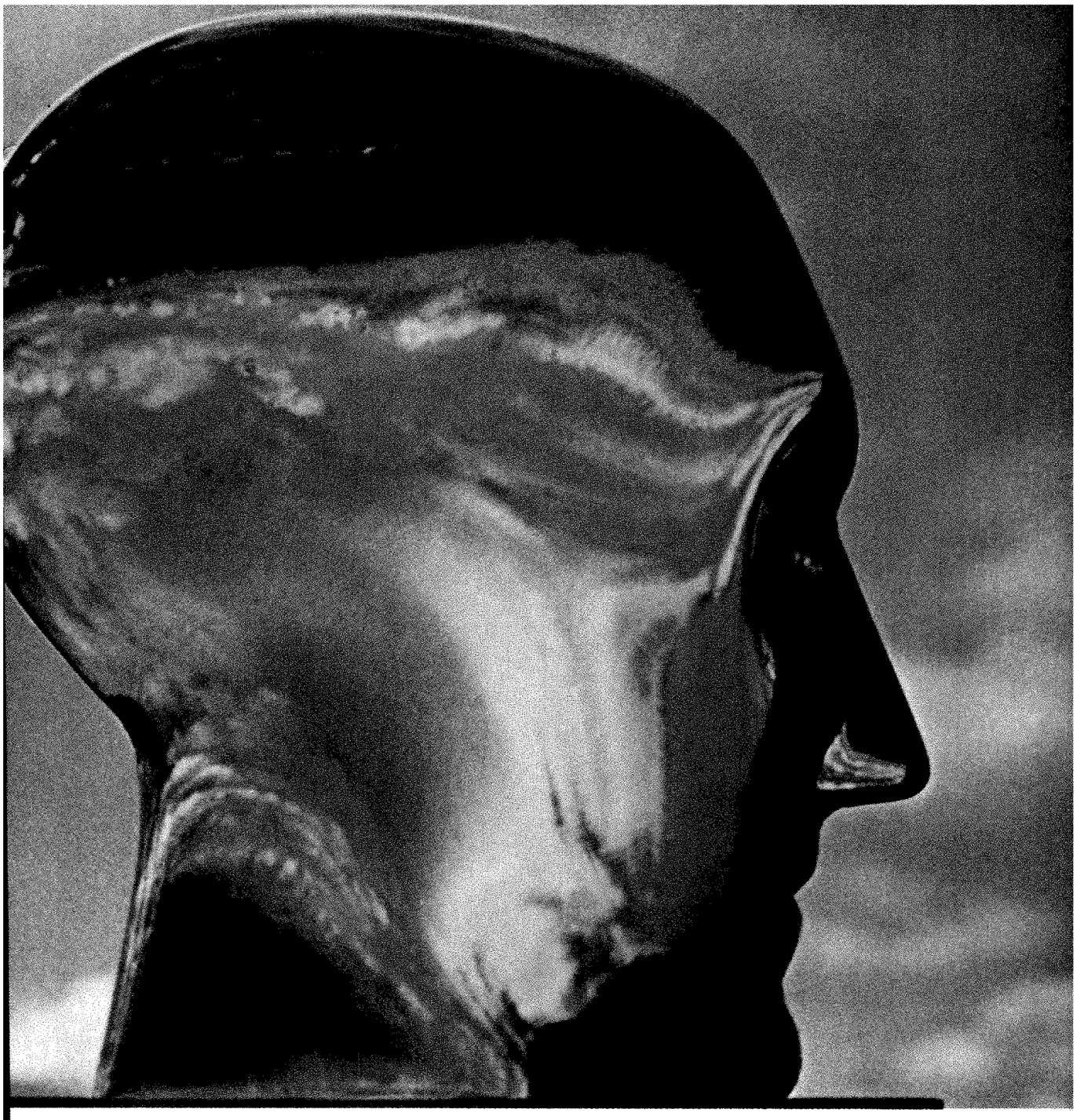
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Combipres.® Today and Tomorrow

well tolerated—only 9% of 484 patients, in 16 clinical trials, definitely or probably dropped out due to side effects.[1]





ffective control in (mild to moderate) hypertension sually with just 2 or 3 tablets daily.

Low incidence of depression, and orthostatic ypotension.*

The most common side effects are dry mouth, rowsiness, and sedation, which generally tend to dim- ish with time. As with other antihypertensives contain- g diuretic agents, hypokalemia, hyperuricemia, and yperglycemia may occur. Drowsiness and sedation ay be alleviated by giving the larger portion of the ivided dose at bedtime.[2,3]

Convenient morning and bedtime dosage cheduling.

Combipres®

Each tablet contains: Catapres* (clonidine HCl) 0.1 or 0.2 mg and chlorthalidone 15 mg

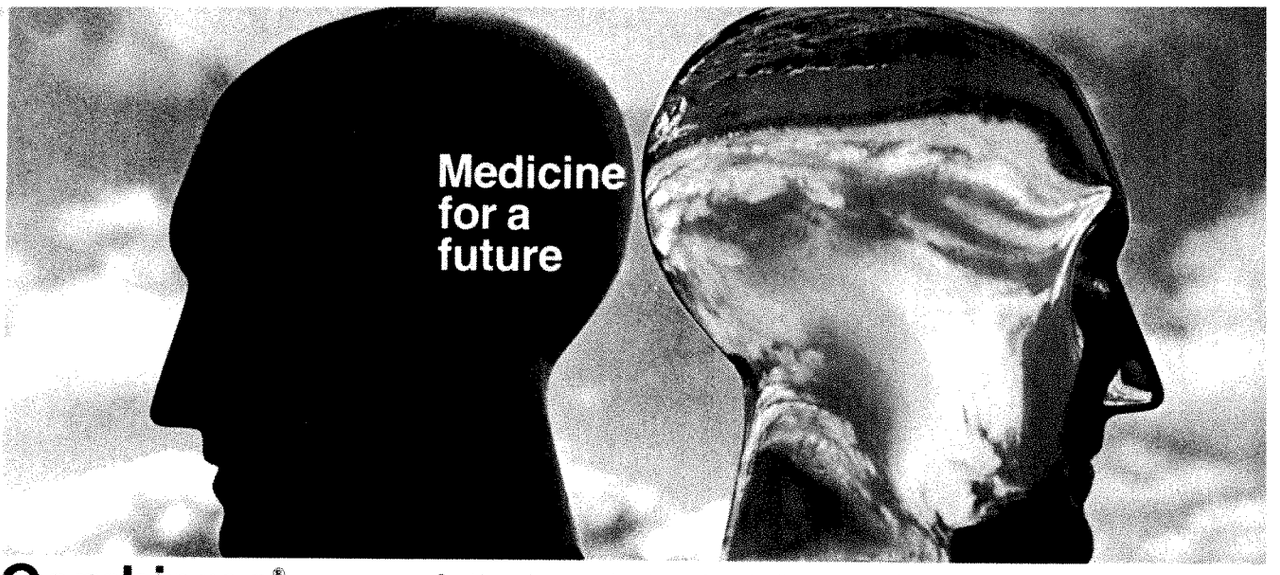
.1 and .2

HYPERTENSION

Combipres is not indicated for initial therapy. It is for patients responsive to its components given separately in equivalent dosages.

Please see brief summary of the prescribing information on the last page of this ad for warnings, precautions, and adverse reactions.

*Orthostatic hypotension has been reported with chlorthalidone and may be potentiated when chlorthalidone is combined with alcohol, barbiturates, or narcotics.



Combipres® .1 and .2

Each tablet contains Catapres* (clonidine HCl) 0.1 or 0.2 mg and chlorthalidone, 15 mg

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres* 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres* 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

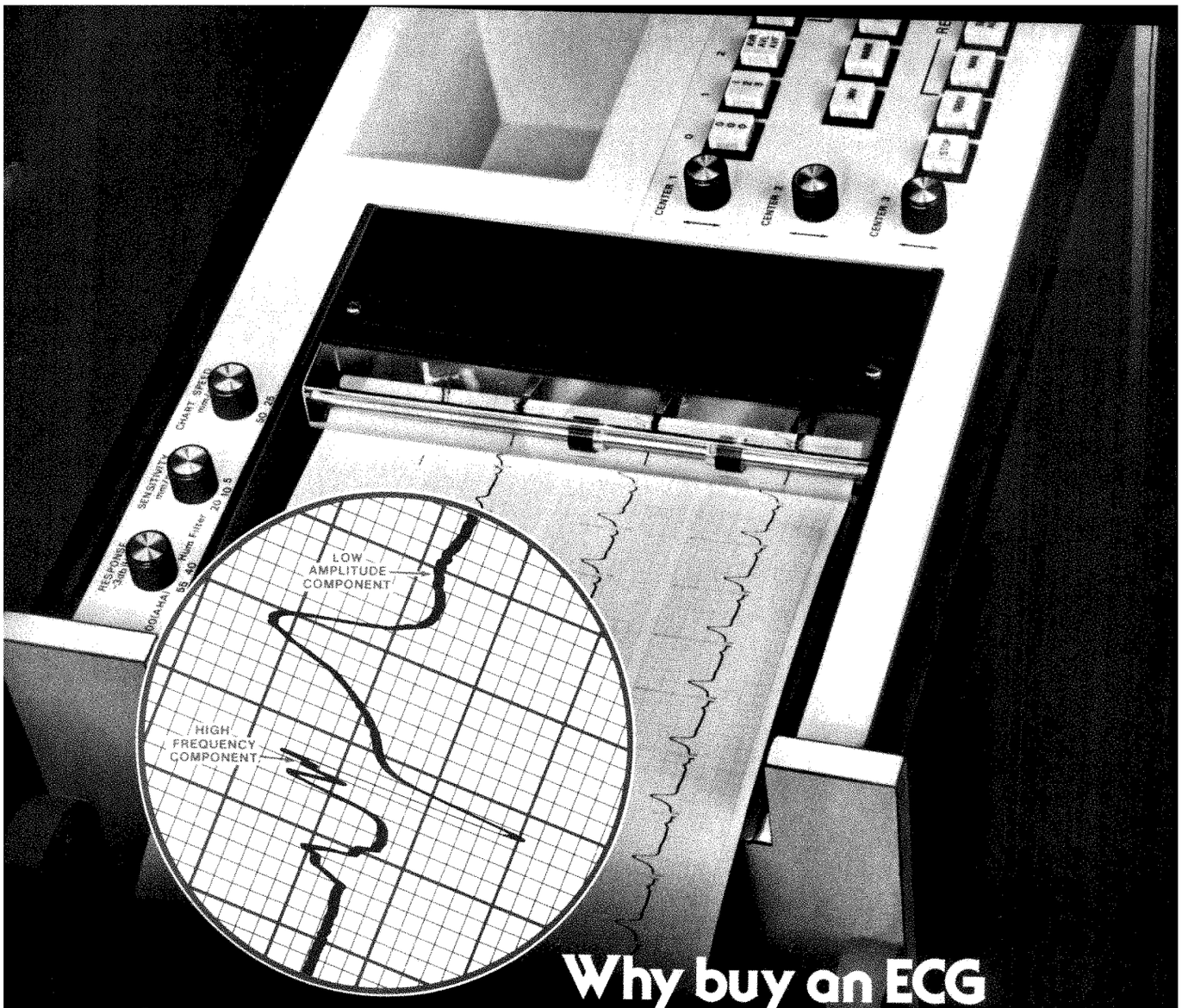
For complete details, please see full prescribing information.

References:

1. Data on file at Boehringer Ingelheim Ltd.
2. Pettinger WA: NEJM, 293:1179, 1975.
3. Katz FH: Hosp Med, 13:34, 1977.

Boehringer Ingelheim

Boehringer Ingelheim Ltd.
Ridgefield, CT 06877



Why buy an ECG if you can't see high-frequency and low-amplitude signals like these?

You can get instruments with good high-frequency response. Or others that can pick up low amplitudes. But would you really trust a diagnosis if you couldn't trust your ECG to do it all?

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Recorder frequency response of more than 200 Hz allows the 3038/2 to respond to high-frequency, low-amplitude signals so small, other ECG's may miss them. A combination of low-friction heated stylus and powerful servo-motor produces tracings so precise, no notches are slurred . . . no vital data lost — even when changes in signal level are less than 10 microvolts (0.1 mm at standard sensitivity).

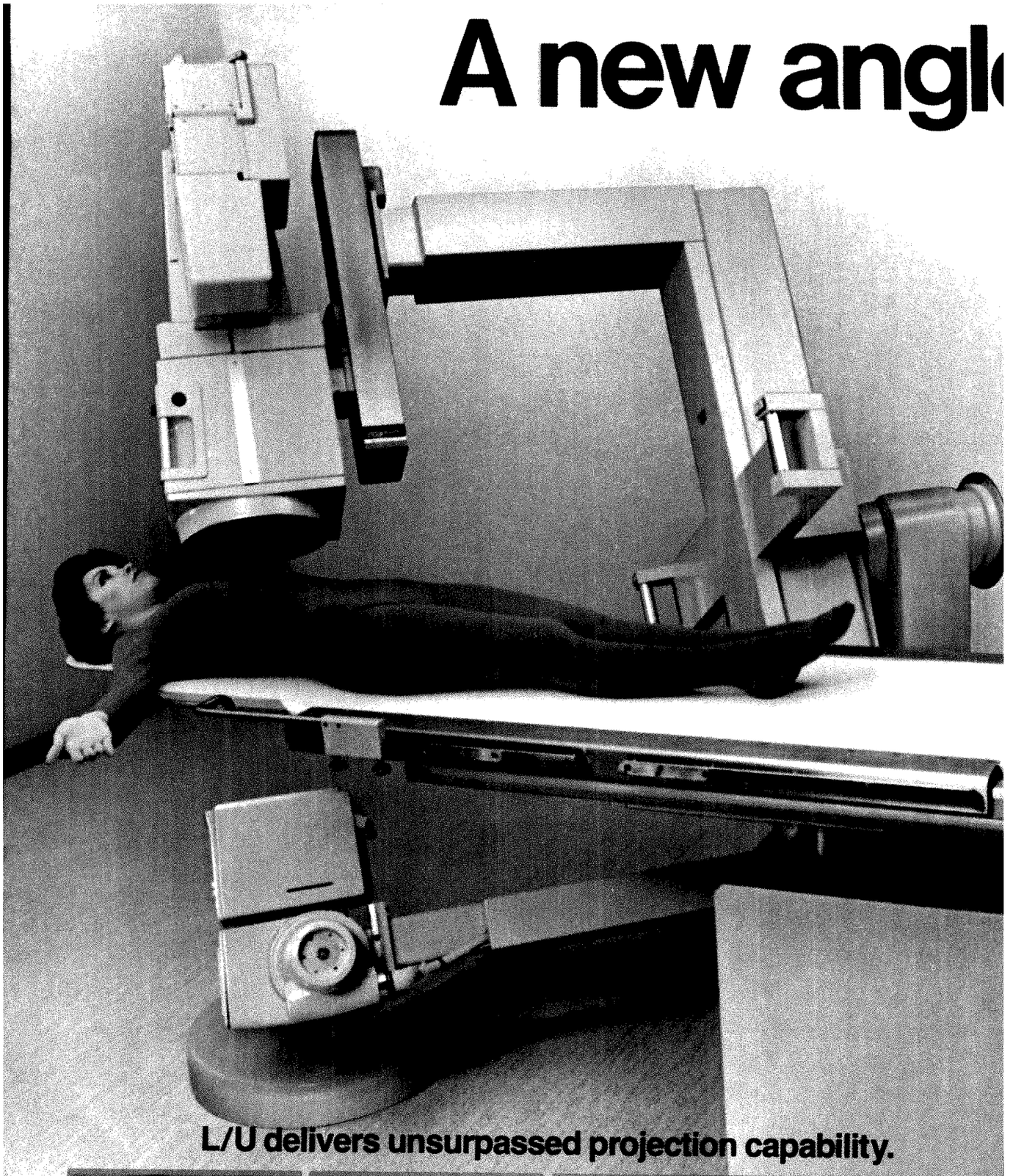
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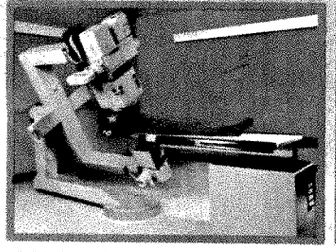
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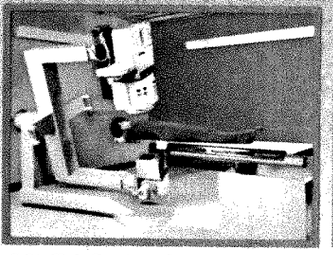
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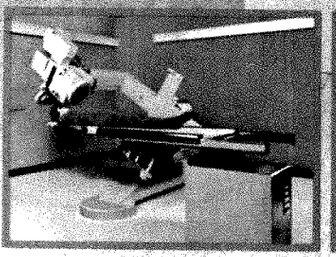
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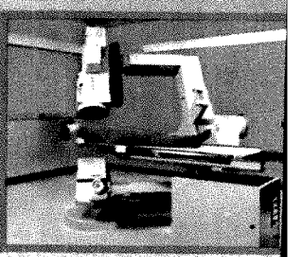
30° RAO



20° RAO, 15° Caudal

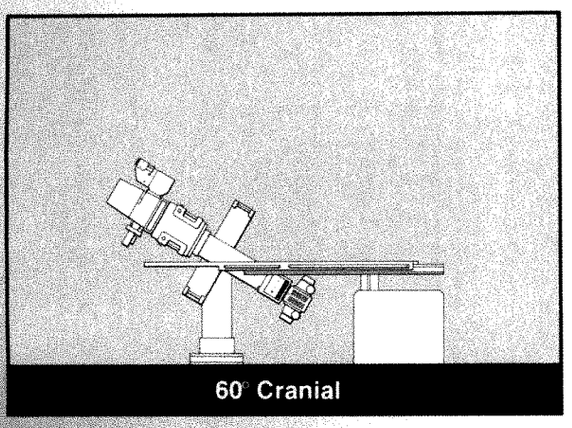


60° Cranial

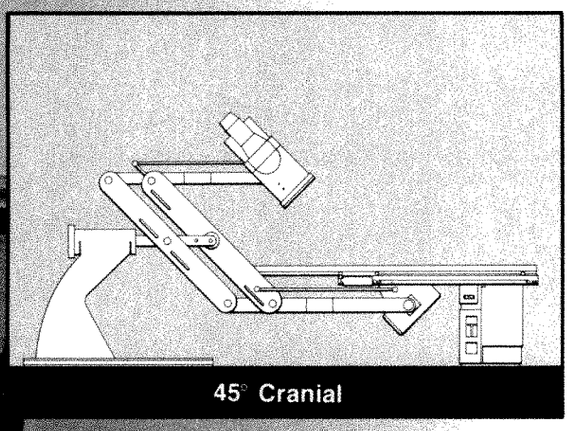


45° LAO, 30° Cranial

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Space-saving design of the new GE system (above) is compared to a conventional unit (below).



GE's new L/U system gives you compact design and motorized positioning.

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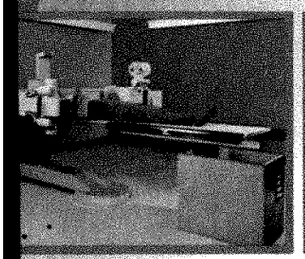
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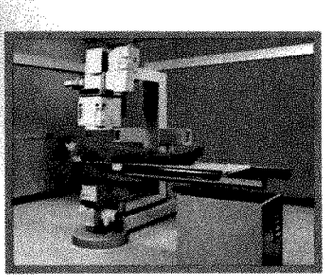
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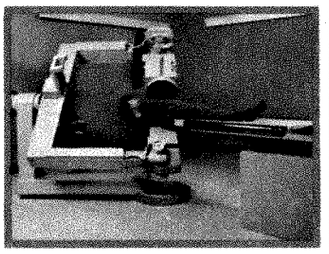
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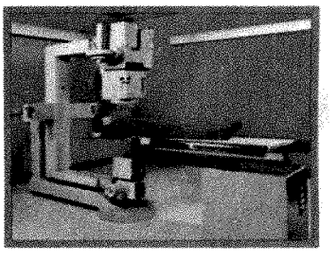
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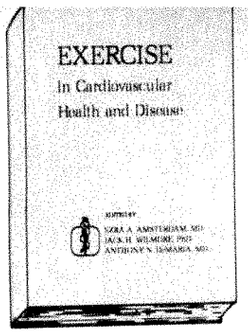
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Lateral


PA


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a **new** publication . . . for **every** professional with an interest in Exercise and the Heart

EXERCISE in Cardiovascular Health and Disease

Edited by
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Jack H. Wilmore, PhD, Professor and Head Dept. of Physical Education & Athletics, Univ. Arizona
Anthony N. DeMaria, MD, Dir. Echocardiography Section, Univ. of Calif. School of Medicine

SEPTEMBER 1977, 408 PAGES, ILLUS.

Just published, this comprehensive work covers every aspect of exercise and its role in **Diagnosis, Treatment,** and **Prevention** of cardiac disease.

The scope of EXERCISE IN CARDIOVASCULAR HEALTH AND DISEASE is so broad that it goes from something as basic as a detailed study of the heart muscle itself to the latest advances in cardiac rehabilitation.

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- ☐ Nuclear cardiology
- ☐ Computer analysis of the exercise ECG
- ☐ Stress myocardial scintigraphy
- ☐ Various interpretations of exercise tests in the asymptomatic population

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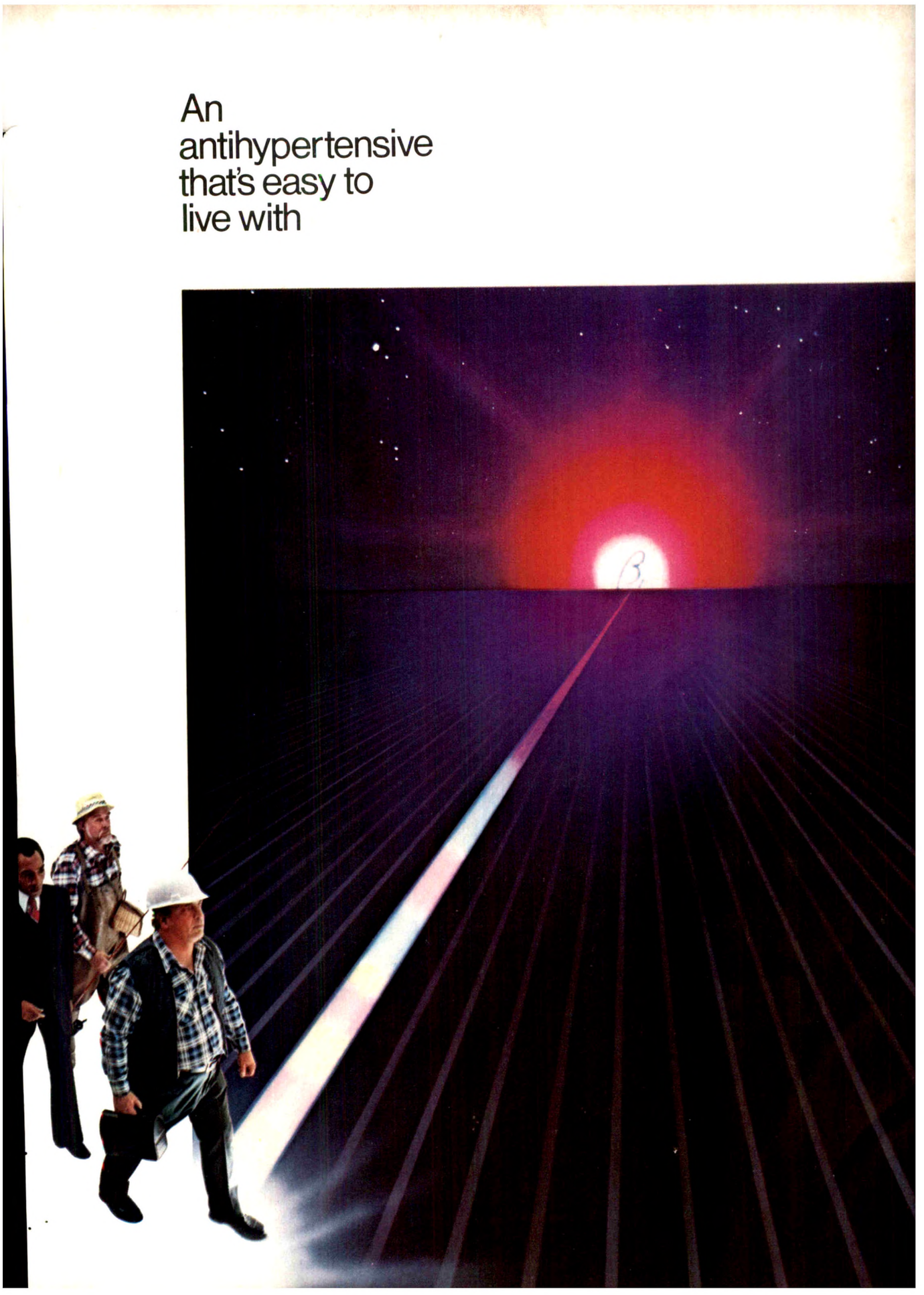
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Patients will also appreciate the easy-to-remember b.i.d. dosage of Lopressor. Since b.i.d. dosage is known to encourage patient adherence, this is another way that Lopressor improves your chances for long-term therapeutic success.

Significantly reduces blood pressure when added to a diuretic.

Lopressor caused a significant fall in blood pressure when given to patients already receiving a diuretic. Investigators reporting in the British Journal of Pharmacology concluded that "Metoprolol in combination with chlorthalidone appears to be an effective and well-tolerated treatment for mild and moderate hypertension in those patients not responding to chlorthalidone alone."*

Treatment Period

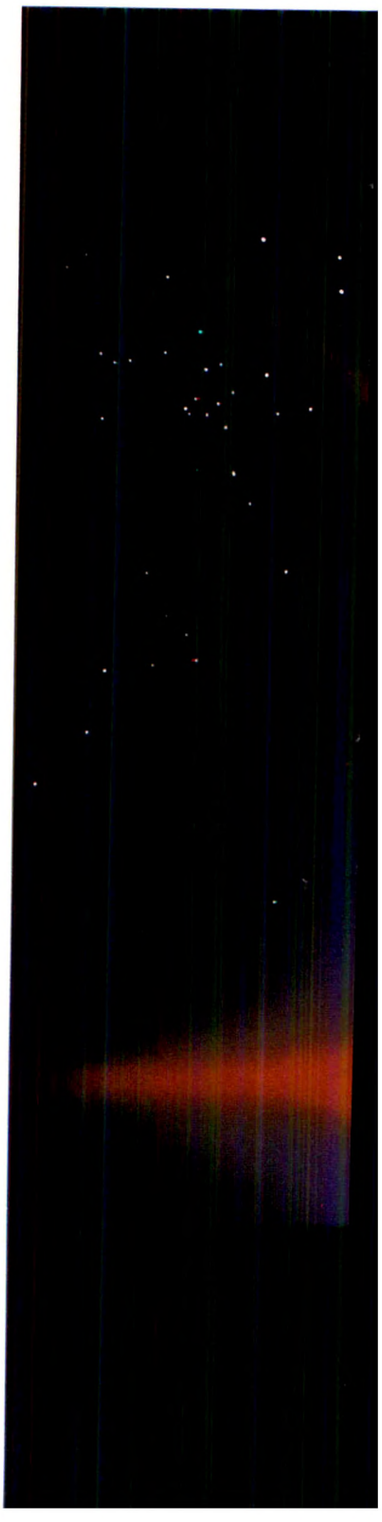
Placebo + chlorthalidone		Metoprolol + chlorthalidone
one month		
Systolic BP (mmHg)		
158±4	supine	142±4
160±5	standing	147±3
Diastolic BP (mmHg)		
96±2	supine	87±1
102±2	standing	94±1
two months		
Systolic BP (mmHg)		
159±4	supine	146±4
159±4	standing	147±4
Diastolic BP (mmHg)		
96±2	supine	89±1
101±2	standing	95±1
three months		
Systolic BP (mmHg)		
158±5	supine	148±3
159±4	standing	149±3
Diastolic BP (mmHg)		
97±2	supine	87±1
101±2	standing	93±1

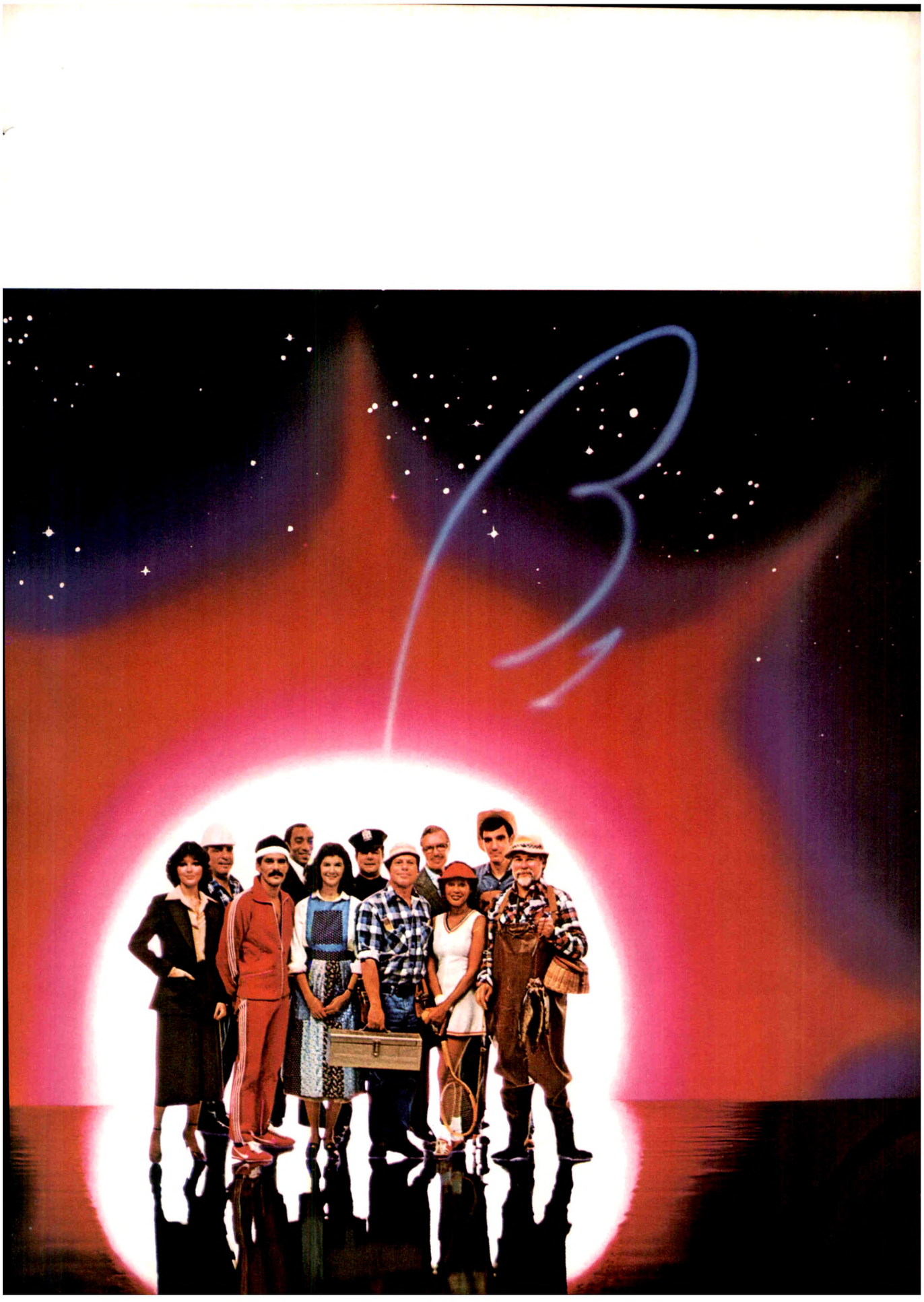
Works primarily where it should... not where it shouldn't.

Lopressor is the only relatively selective beta blocker available in the United States. Unlike the first generation beta blocker, propranolol, which is nonselective, Lopressor has a preferential effect on beta receptors involved in lowering blood pressure. It has less effect on beta receptors that do not relate to antihypertensive mechanisms.

Please see last page of this advertisement for brief summary of prescribing information.

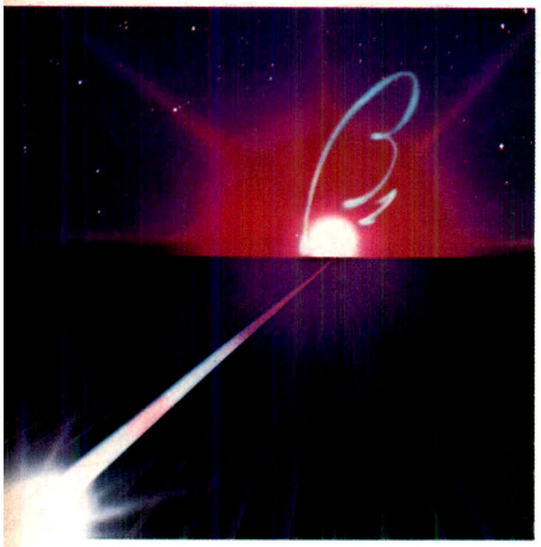
*Jäättelä A, Pyörälä K: A controlled study on the antihypertensive effect of a new β-adrenergic receptor blocking drug, metoprolol, in combination with chlorthalidone. Br J Pharmacol 3:655-660, 1976.





The relatively selective beta blocker for hypertension.

Lopressor™
metoprolol tartrate



Lopressor™
brand of metoprolol tartrate

An antihypertensive beta-blocking agent

Indications Lopressor, brand of metoprolol tartrate, is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor, brand of metoprolol tartrate, is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor, brand of metoprolol tartrate, should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor, brand of metoprolol tartrate, therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor, brand of metoprolol tartrate, should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor, brand of metoprolol tartrate, may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in three doses daily, instead of two, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor, brand of metoprolol tartrate, should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor, brand of metoprolol tartrate, plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor, brand of metoprolol tartrate, should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, Raynaud's disease, palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 o 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor, brand of metoprolol tartrate, during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor brand of metoprolol tartrate, should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughou the day. If control is not adequate, a larger dose, o three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor, brand of metoprolol tartrate, is increased.

This drug should be stored at controlled room tem perature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

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Comparison of Treadmill Exercise Testing and Psychologic Stress Testing Soon After Myocardial Infarction

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CRAIG BARR TAYLOR, MD
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Stanford, California

Are physical or psychologic stressors more useful for evaluating psychologic stress in patients with coronary heart disease? To evaluate this question, patients underwent physical and psychologic testing 7 weeks after myocardial infarction. The psychologic stress test consisted of an open-ended interview, a videotape depicting stressful scenes and a puzzle task. In 20 men whose mean age ± standard deviation was 52 ± 1 years, the interview produced the following peak heart rate and systolic blood pressure responses: 83 ± 18 beats/min and 140 ± 13 mm Hg, which were 8 and 10 percent, respectively, above values at rest ($P < 0.05$). Symptom-limited treadmill exercise testing in 10 of these patients elicited maximal heart rate and systolic blood pressure values of 152 ± 24 beats/min and 172 ± 32 mm Hg, respectively; ischemic S-T segment depression or angina pectoris occurred in 6 of the 10 patients, whereas none had demonstrated ischemia with psychologic testing. A second consecutive series of 20 patients demonstrated cardiovascular responses to physical and psychologic stress similar to those of the first series. Again, ischemic abnormalities were absent during psychologic stress, whereas exercise-induced ischemic abnormalities were noted in 3 of 20 patients. Ischemic abnormalities are unlikely to appear during psychologic stress testing in patients with a high heart rate and systolic blood pressure threshold for ischemic abnormalities during exercise testing. Standard methods of physical exercise testing are superior to currently available psychologic stress tests for evaluating the cardiovascular response to most commonly encountered psychologic stressors.

Exercise testing is increasingly used to evaluate prognosis and to establish guidelines for resumption of physical and sexual activity after myocardial infarction.[1–3] However, even in patients free of effort-induced ischemic abnormalities, there is concern that exposure to psychologic stress may precipitate subsequent coronary events.[4,5] A psychologic stress test capable of safely and reliably eliciting significant cardiovascular abnormalities would appear to be useful in evaluating the readiness of patients to resume "stressful" activities after infarction, especially if such testing elicited abnormalities that were not disclosed by standard techniques such as exercise testing and ambulatory electrocardiography.

Schiffer et al.[6] reported that a psychologic stress "quiz electrocardiogram" elicited ischemic S-T segment abnormalities in patients with angina pectoris. However, in their patients, the prevalence of ischemic S-T segment abnormalities was greater with the physical stress of exercise testing than with psychologic stress testing. Hence, it is not clear that psychologic stress testing provides a sufficient yield of independent information to be clinically useful.

We designed this study to answer the following questions: (1) Which forms of psychologic stress testing are most useful in eliciting a significant

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cardiovascular response soon after myocardial infarction? (2) What is the relative utility of treadmill testing and psychologic stress testing in eliciting a significant cardiovascular response and in disclosing cardiovascular abnormalities in patients recovering from myocardial infarction?

Methods

Study patients: The patients were participants in a long-term follow-up study of recovery from myocardial infarction. All had performed treadmill exercise testing 3 weeks after infarction. Patients were considered eligible to perform this test if they were aged 70 years or less and had no clinical heart failure or unstable angina pectoris 3 weeks after infarction. All patients were employed at the time of infarction. Three-quarters described their work as "professional, managerial, sales," 15 percent as "clerical, craftsman" and 10 percent as manual labor. No formal exercise training or psychologic counseling was provided to patients during the study period. No patient declined to undergo psychologic testing.

Twenty consecutive patients participated in the first phase of this study (Experiment I) 7 weeks after infarction. This phase was designed to compare the cardiovascular effects of treadmill testing and psychologic stress testing. The mean age (± standard deviation) of these patients was 52 ± 1 years. The myocardial infarction was anterior in 5 patients, inferior in 14 and nontransmural in 1 patient. Cardiac medications were quinidine, 400 mg/day (1 patient); propranolol, 80 mg/day (2 patients) and quinidine, 800 mg/day plus propranolol, 80 mg/day (1 patient).

The next 20 consecutive patients participated in the second phase of this study (Experiment II) 7 weeks after infarction. This phase was designed to provide a more standardized psychologic stress. The mean age of these patients was 54 ± 1 years. The myocardial infarction was anterior in 7 patients, posterior in 11 and nontransmural in 2. Cardiac medications were procainamide, 1 g/day (1 patient) and 2 g/day (1 patient) and propranolol, 80 mg/day (1 patient).

Psychologic tests: All subjects completed a battery of psychologic tests designed to reflect problems commonly encountered after myocardial infarction. The tests consisted of the Zung or Beck Depression Scales,[7] the State-Trait Anxiety Inventory,[8] the Profile of Mood States[9] and the Cardiac Adjustment Scale.[10] The first three tests were designed to measure various moods including depression and anxiety. The fourth test has been developed to reflect overal adjustment to myocardial infarction.

After completion of the psychologic tests, the subjects wen to an examination room, 10 feet by 10 feet, where a blooc pressure cuff and electrocardiographic leads were applied Electrocardiographic recordings were made on a Physiograph projector model type PMP-4A, E & M Instrument Company Blood pressure was recorded by an Arteriosonde (Roche mode 1216) automatic blood pressure measuring device. During the entire stress test, electrocardiographic rhythm strips wer recorded during the last 6 seconds of every minute and blooc pressure was recorded during the middle of each minute Leads V_4 to V_6 of the electrocardiogram were monitored or an oscilloscope during the entire experiment. The psychologic stress test of Experiment I had five components. The orde of these components was varied to control for possible sequence effects, as depicted in Table I.

Baseline (5 minutes): During this period patients were asked to sit quietly in an armchair. No stressful stimuli were presented and no specific instructions for relaxation were given.

Interview (20 to 30 minutes): The interview consisted of a series of standardized questions designed to probe areas of potential concern to postinfarction patients. Although the questions were standardized, the length of each interview varied, depending on the content and depth of the subject's responses. Topics included effects of myocardial infarction on the patient's prospects for the future, including job and financial status, sex life and physical capabilities. All interviews were conducted by the same person, a clinical psychologist.

Videotape (15 minutes): The videotape consisted of three potentially stressful scenes: a man having a heart attack and being rushed to the hospital in an ambulance, a child suffocating and a young couple having explicit sex.

Puzzle (5 minutes): Patients were asked to assemble a geometric puzzle within 3 minutes. The task was presented as simple, although few persons could complete it in 3 minutes. Elapsed time was called out periodically and the interviewer made time-pressure remarks while the subject worked.

Relaxation training: After completion of two of the preceding three procedures (interview, videotape, puzzle), the patients were instructed in a relaxation technique. While sitting quietly, they were given a series of relaxation exercises based on Jacobson's deep muscle relaxation technique. Instructions were prerecorded on an audiotape and consisted of training in muscle tension and relaxation followed by deep breathing and repetition of a word or phrase. Relaxation training required 10 minutes. After the last of the three stressors, a 5 minute period of relaxation was provided.

Because cardiovascular responses to the videotape were less than to the puzzle and because videotapes have been shown to have adverse psychologic effects,[1] the videotape was eliminated from Experiment II (Table I). In addition, the puzzle task was extended to determine whether greater exposure to this stressor would evoke a greater cardiovascular response. Four puzzle completion tasks were taken from the Wechsler Adult Intelligence Scale test. Patients were given a limited time (3 minutes) to complete each of the puzzles. The interview was abbreviated and standardized. The experimenter, a graduate student in psychology, presented a list of questions in a matter-of-fact way without attempting to pursue topics that appeared to be particularly troublesome to the patient. The order of presentation was again randomly varied to control for sequence effects, and relaxation was performed only after both stressors had been presented. All patients were carefully debriefed after the psychologic stress tests to alle-

TABLE I

Order of Psychologic Stress Test Procedures, Experiments I and II

	Time (min)												
	0	5	10	15	20	25	30	35	40	45	50	55	60
Experiment I													
B	I					V			R_1	P_1	R_2		
B	V				P_1	R_1			I			R_2	
B	P_1		I				R_1		V			R_2	
Experiment II													
B	I						P_1		P_2			R_1	
B	P_1		P_2				I					R_1	

B = baseline; I = interview; P_1, P_2 = puzzle 1, puzzle 2; R_1, R_2 = 1st, 2nd relaxation period; V = videotape.

TABLE II

Cardiovascular Responses to Psychologic Stress Testing (mean ± standard deviation)

	Experiment I					
	Base-line	Inter-view	Video Tape	R_1	Puzzle	R_2
Max HR	78 ± 13	83 ± 18†	83 ± 13†	81 ± 18	84 ± 18†	76 ± 13
Max SBP	127 ± 13	140 ± 13†	135 ± 13†	130 ± 13	137 ± 13†	128 ± 9
Max DBP	88 ± 13	105 ± 9†	99 ± 13†	92 ± 13	100 ± 18†	92 ± 9
Max $\frac{HR \cdot SBP}{100}$	95 ± 18	113 ± 22†	108 ± 18†	100 ± 22	112 ± 22†	95 ± 18
Mean HR	74 ± 13	77 ± 13*	74 ± 13	73 ± 13	81 ± 18†	72 ± 13
Mean SBP	121 ± 9	132 ± 9†	128 ± 9†	122 ± 9	133 ± 9†	123 ± 9
Mean DBP	83 ± 9	92 ± 9†	88 ± 9*	85 ± 9	92 ± 13†	86 ± 13
Mean $\frac{HR \cdot SBP}{100}$	79 ± 18	101 ± 18†	94 ± 18*	89 ± 22	107 ± 22†	90 ± 18

	Experiment II				
	Base-line	Inter-view	$Puzzle_1$	$Puzzle_2$	R_1
Max HR	83 ± 13	88 ± 13†	86 ± 13†	90 ± 18†	82 ± 13
Max SBP	123 ± 13	134 ± 13†	128 ± 13	135 ± 13†	126 ± 13
Max DBP	84 ± 9	95 ± 13†	89 ± 13	98 ± 13†	91 ± 13
Max $\frac{HR \cdot SBP}{100}$	100 ± 22	113 ± 22†	107 ± 22	116 ± 18†	99 ± 18
Mean HR	80 ± 13	79 ± 13	81 ± 13*	83 ± 13†	76 ± 13
Mean SBP	120 ± 13	122 ± 13	121 ± 13	121 ± 9	117 ± 9
Mean DBP	81 ± 9	84 ± 13	84 ± 13	83 ± 9	80 ± 9
Mean $\frac{HR \cdot SBP}{100}$	99 ± 18	97 ± 18	99 ± 18	100 ± 18	89 ± 18

* $P < 0.05$ compared with baseline value; † $P < 0.005$ compared with baseline value.
DBP = diastolic blood pressure (mm Hg); HR = heart rate (beats/min); max = maximal; R_1 and R_2 = relaxation period 1 and 2, respectively; SBP = systolic blood pressure (mm Hg).

viate any concerns they may have had and to ascertain whether they experienced any adverse effects from the procedures.

Exercise testing: After psychologic stress testing, patients underwent symptom-limited treadmill exercise testing, utilizing a combination of Naughton and Balke protocols.[12] Tests were stopped because of 1) limiting symptoms of angina, dyspnea, fatigue, 2) a decrease in systolic blood pressure greater than 10 mm Hg from the peak value noted earlier during exercise, or 3) the appearance of ventricular tachycardia. Ischemic S-T segment depression alone was not an end point. Ischemic S-T segment abnormality was defined as flat or downsloping depression of 0.1 mv or more below the P-R segment 0.08 second after the J point.

Results

Cardiovascular responses to psychologic testing: The levels of anxiety or depression indicated on the Zung, Beck, Spielberger or Profile of Mood States were not significantly different from those of normal populations. Detailed reports of the psychologic test results will be reported elsewhere.

Maximal and mean values for heart rate, systolic and diastolic blood pressure and heart rate-systolic blood pressure product ("double product") increased significantly from the baseline value during the interview and puzzle phases of Experiment I (Table II, Fig. 1). Lesser increases were noted for the responses to the videotape, although all responses to this stress except that of mean heart rate were statistically significant. Both relaxation periods lowered cardiovascular variables to baseline values. The patients described the videotape, puzzle and interview as only "mildly" upsetting, and none reported any adverse effects. Although the heart rate and systolic blood pressure responses of patients in Experiment II exceeded those of patients in Experiment I, there were no significant differences in mean or maximal heart rate

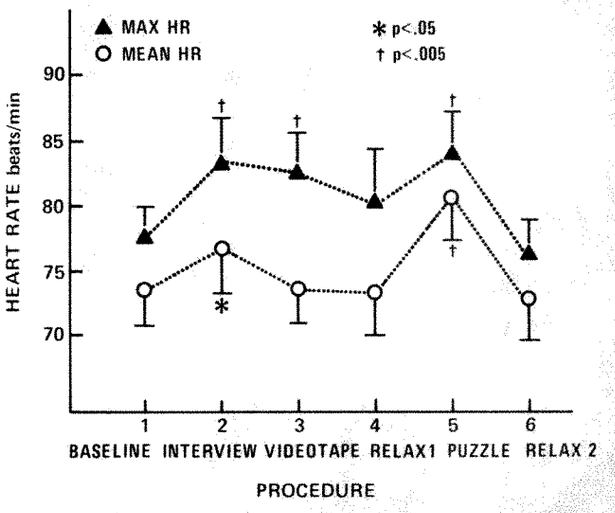


FIGURE 1. Heart rate (HR) response to psychologic stress testing (Experiment I). Values are expressed as mean ± standard error of the mean. MAX = maximal; p = probability; RELAX 1 and RELAX 2 = first and second relaxation periods, respectively.

responses during the most stressful procedure performed by each of these two groups. The prolonged puzzle task of Experiment II produced slightly greater changes in heart rate, blood pressure and double product than the shorter puzzle of Experiment I (Table II, Fig. 2). The structured interview of Experiment II produced a slightly lesser cardiovascular response than did the open-ended interview of Experiment I. Neither ischemic S-T segment depression nor angina pectoris was noted with psychologic stress testing in Experiment I or Experiment II.

Cardiovascular response to treadmill exercise: All 20 patients in Experiment I had a treadmill exercise test 3 weeks after infarction. The last half of this group underwent repeat treadmill exercise testing at 7 weeks. The treadmill performance at 3 weeks was not significantly different in those who subsequently had a 7 week test and those who did not. The mean maximal heart rate was 133 ± 12 beats/min, mean maximal systolic pressure 171 ± 16 mm Hg and mean maximal workload 5.9 ± 1.5 METs (multiples of estimated resting metabolic requirement).

Treadmill exercise testing was performed 7 weeks after infarction by the last 10 patients participating in Experiment I. These patients demonstrated a mean maximal heart rate of 152 ± 33 beats/min, mean maximal systolic blood pressure of 172 ± 44 mm Hg and a mean maximal work load of 8.3 ± 2.2 METs. Exercise-induced ischemic S-T segment depression appeared in 6 of 10 patients, 2 of whom experienced angina pectoris. "Complex" ventricular ectopic activity (bigeminy, couplets or four or more ventricular premature complexes/min) was noted in four patients.

The 20 patients participating in Experiment II who underwent treadmill exercise testing 7 weeks after infarction had a mean maximal heart rate of 148 ± 16 beats/min, mean maximal systolic blood pressure of 173 ± 21 mm Hg and mean maximal work load of 9.1 ± 2.1 METs. Ischemic S-T segment abnormality was noted in three patients, simple ventricular ectopic activity in four patients and complex ventricular ectopic activity in three patients. Thus, heart rate and blood pressure responses to treadmill exercise were similar, but patients in Experiment I tended to show a greater prevalence of exercise-induced ischemic S-T segment depression and ventricular ectopic activity than patients in Experiment II.

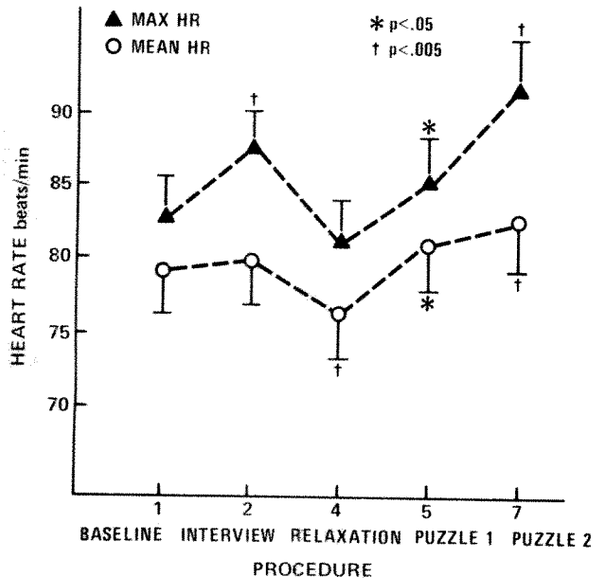


FIGURE 2. Heart rate (HR) response to psychologic stress testing (Experiment II). Abbreviations as in Figure 1.

Comparison of cardiovascular responses to psychologic and physical stress: Cardiovascular values recorded during psychologic stress were substantially lower than those noted during treadmill exercise testing ($P < 0.001$) (Table III). Heart rate and systolic blood pressure responses at the onset of ischemic S-T segment depression were substantially greater during treadmill exercise than during psychologic stress testing (Table IV).

Discussion

The goal of psychologic stress testing in postinfarction patients is the safe and reliable demonstration of cardiovascular abnormalities that are predictive of subsequent coronary events. As a first step toward this goal, we sought to develop a simple method for eliciting a significant cardiovascular response in a group of patients who had recently experienced a myocardial infarction. We presented stimuli that would be expected to elicit a significant cardiovascular response, whether or not the stimuli were typical of those that might be encountered under usual circumstances. Although our patients demonstrated statistically significant increases in heart rate, blood pressure and heart rate-systolic pressure product in response to psychologic stress procedures, no ischemic S-T segment abnormalities or cardiac symptoms were noted, although they were found in 9 of the 30 patients undergoing exercise testing. This disparity in the diagnostic yield of the two methods is not surprising because the "threshold" of heart rate and systolic blood pressure at the onset of ischemic S-T segment depression or angina pectoris with treadmill exercise was substantially higher than the peak values noted during psychologic stress testing. Similarly, only two of our nine patients with ischemic S-T segment depression manifested this abnormality at or below the peak double product of 176 observed in Schiffer's normotensive patients.[6]

Ischemic responses to psychologic versus exercise testing: The heart rate-systolic pressure product is an important hemodynamic accompaniment of ischemic abnormalities in patients with chronic ischemic heart disease. Robinson[13] noted a reproducible heart rate and systolic blood pressure at which angina pectoris occurred in response to physical effort and psychologic stress within the laboratory. Littler et al.[14] extended these observations to men undergoing ambulatory electrocardiography outside the laboratory. Gobel et al.[15] recently demonstrated that heart rate

correlates well with coronary blood flow and myocardial oxygen consumption in patients with angina pectoris and ischemic S-T segment depression.

Thus, the ability of psychologic or physical tests to elicit ischemic abnormalities reflects their capacity to produce an imbalance between oxygen supply and demand in a given patient. Psychologic stress testing did not elicit such a response in our patients. The magnitude of cardiovascular responses to stress noted in our patients and in other studies[16,17] is similar to that noted by Schiffer et al.,[6] who administered a quiz electrocardiogram consisting of a 20 minute tape-recorded series of questions to 20 patients with a history of angina pectoris. Although these investigators noted a good correlation between the *extent* of ischemic S-T segment depression induced by quiz electrocardiography and by submaximal bicycle exercise, the *prevalence* of ischemic S-T segment abnormalities and angina pectoris was substantially greater with bicycle exercise testing than with psychologic stress testing. Schiffer et al. did not indicate the heart rates and systolic blood pressures at which S-T segment depression and angina pectoris appeared in their patients. Thus, it appears that the greater yield of ischemic abnormalities with psychologic stress testing noted by Schiffer et al. primarily reflects a greater extent of disease than was evident in our patients: Their patients were selected because of a history of angina pectoris, whereas angina was present in only 3 of our 30 patients, even with the stress of treadmill exercise.

The extent of cardiovascular changes produced by the stressful stimuli in our study was similar to that reported by investigators using similar stimuli.[16,17] Hence, it is unlikely that modification of our stress test would have greatly altered the outcome in our patients. More extreme stressors such as parachute jumps,[18] prolonged and intensive interviews,[19] sensory stimulation and isolation and fatigue situations[20] have been used to elicit stress. Although these stressors elicit substantial cardiovascular changes, they are neither feasible nor appropriate in the evaluation of patients with chronic ischemic heart disease.

Standardized laboratory stress tests do not replicate an individual subject's response to the multitude of environmental stressors that may elicit a major cardiovascular response. On the other hand, the use of severe laboratory stressors such as prolonged fatigue is neither practical nor ethically justifiable in a clinical setting.

Response to exercise stress testing as a measure of response to psychologic stress: Measurement of the cardiovascular tolerance for psychologic stress is usually considered in the context of a psychologic stimulus eliciting a cardiovascular response. A major shortcoming of this approach is the difficulty of presenting a psychologic stimulus that is sufficiently powerful to pose a significant challenge to the cardiovascular system—one that might provide a reliable measure of the heart's response to severe psychologic stress. However, in another approach to this problem, one can consider the cardiovascular response to a severe physical challenge without attempting to provide a psychologic stimulus. The absence of significant cardiovascular abnormalities during symptom-limited exercise testing, for example, would provide some assurance that other challenges to the cardiovascular system including psychologic stress would likewise not elicit major cardiovascular abnormalities. The important observations of Robinson[13] and Littler et al.[14] are pertinent to this question: These investigators noted that angina pectoris tended to occur at a similar heart rate in response to psychologic as well as to physical stress. If the same were true for ischemic S-T segment depression, then psychologic stress testing could be obviated in favor of more standardized and familiar forms of exercise testing. In fact, exercise testing has long been used to provide guidelines for cardiac patients to engage in sexual intercourse, an activity in which psychologic factors may play a large part in the cardiovascular response.[3,21] Hellerstein and Friedman[3] observed that the mean maximal heart rate during intercourse was approximately 118 beats/min, representing an energy expenditure of only 60 percent of maximal oxygen consumption. Patients capable of completing a double Master test usually experience no significant cardiovascular limitation during sexual intercourse. On the other hand, most coital deaths appear

TABLE III

Peak Cardiovascular Responses to Psychologic Stress and Treadmill Exercise (mean ± standard deviation)

Peak Response	Experiment I		Experiment II	
	Puzzle (no. = 10)	Treadmill (no. = 10)	Puzzle (no. = 20)	Treadmill (no. = 20)
HR	93 ± 9	152 ± 8	86 ± 3	148 ± 5
SBP	127 ± 14	172 ± 10	128 ± 3	173 ± 7
$\frac{HR \cdot SBP}{100}$	117 ± 20	265 ± 23	107 ± 5	255 ± 15

HR = heart rate (beats/min); SBP = systolic blood pressure.

TABLE IV

Cardiovascular Responses in Patients With Exercise-Induced Myocardial Ischemia

Exp	Patient Age (yr)	HR at ST↓	SBP at ST↓	HR·SBP/100 at ST↓	Max ST↓	Angina
I	51	150	166	249	−0.15	No
I	57	130	140	182	−0.10	No
I	55	150	196	294	−0.10	No
I	56	165	174	287	−0.10	No
I	52	110	135	149	−0.20	Yes
I	55	110	168	185	−0.50	Yes
II	56	130	144	187	−0.20	Yes
II	62	160	110	176	−0.10	No
II	59	135	176	238	−0.20	No
Mean ± SD	56 ± 4	138 ± 20	157 ± 26	216 ± 52	0.17 ± 0.13	

Exp = experiment; HR = heart rate; max = maximal; SBP = systolic blood pressure (mm Hg); SD = standard deviation; ST↓ = ischemic S-T segment depression (mv).

to occur during extramarital sexual activity.[22] This suggests that psychologic factors that cannot be simulated by physical work tasks may be of great significance apart from the physical stress of intercourse with a married partner. Similarly, patients with good tolerance for physical exercise may experience angina pectoris predominantly or exclusively with psychologic stress. The mechanisms responsible for this disparity are not well understood.

Implications: Although a physical stress does not simulate psychologic stress, it appears to provide a useful measure of the cardiovascular response that would be elicited by most but not all physical and psychologic stressors. The absence of significant cardiovascular abnormalities with treadmill exercise testing does not exclude the existence of significant myocardial ischemia and its clinical consequences during severe psychologic stress. Like any laboratory test, exercise testing is not perfect. However, it does appear superior to currently available psychologic stress tests designed to elicit significant ischemic abnormalities, especially in patients with good exercise tolerance. Moreover, either physical or psychologic stress testing appears to provide a more rational basis for counseling patients with respect to psychologic stress than does the vague and anxiety-provoking advice often given to patients after infarction that they should "take it easy."

Acknowledgment

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Right Ventricular Apical Activation Times in Patients With Conduction Disturbances Occurring During Acute Transmural Myocardial Infarction

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His bundle and right ventricular apical electrograms were recorded in 18 patients with acute transmural myocardial infarction in whom catheter insertion was considered necessary for clinical reasons. The V-RVA and H-V intervals were of normal duration (5 to 30 and 35 to 55 msec, respectively) in five patients (Group 1) with persistently narrow (less than 100 msec) QRS complexes. In contrast, 13 patients (Group 2) who manifested a "complete" right bundle branch block pattern within 96 hours after admission had prolonged V-RVA intervals (range 50 to 80 msec, mean 59.2 msec) and H-V intervals that were at the upper limits of normal or prolonged (range 55 to 90 msec, mean 63 msec). In 6 of these 13 patients, the duration of the V-RVA interval became normal when the "complete" right bundle branch block pattern disappeared and was replaced by a "complete" left bundle branch block pattern in three patients and by narrow QRS complexes in the three other patients.

This study showed that transmural myocardial infarction in itself did not increase the duration of the V-RVA interval even when "complete" left bundle branch block was present. Moreover, a prolonged V-RVA interval coexisting with a "complete" right bundle branch block pattern was not due to distal right bundle branch block but resulted from a conduction disturbance located in the proximal portions of the right bundle, or perhaps, even within the His bundle itself.

Intracavitary electrograms have been used to analyze the arrival of excitation in various ventricular sites and to determine the level (proximal, distal or terminal) of conduction disturbance within the right bundle branch in otherwise normal persons, as well as in patients with chronic conduction system disease or surgically corrected (or noncorrected) congenital cardiac malformations.[1–9] Such studies have not been performed in the acute phase of myocardial infarction. Therefore, it appeared of interest to evaluate the information obtained from recording filtered intracardiac electrograms while placing temporary catheter electrodes for prophylactic demand pacing in patients with acute myocardial infarction.

Methods

Patients: The study population consisted of 18 patients with an acute transmural myocardial infarction who were admitted with narrow (less than 100 msec) ventricular complexes. Five patients (Group 1) had persistently narrow QRS complexes. Thirteen patients (Group 2) manifested a transient or persistent electrocardiographic pattern of "complete" right bundle branch block while under observation in the coronary care unit. All 18 patients had clinical, laboratory and electrocardiographic evidence of evolving transmural myocardial infarction. Their ages ranged between 32 and 82 years (mean 60.5 years, Tables I and II); 15 were men and 3 were women.

Electrocardiographic location of the myocardial infarction was based on the leads in which the abnormal Q waves subsequently appeared (Tables I and II). The surface electrocardiographic pattern of "complete" right bundle branch

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TABLE I

Group 1: Intervals Measured in Patients With Persistently Narrow (100 msec or less) QRS Complexes

Case no.	Age (yr) & Sex	Site of MI	Intervals (msec)* A-H (55–120)	H-V (35–55)	V-RVA (5–30)	H-RVA (40–85)
1	53F	AS	160	55	20	75
2	61M	IP	AB	45	10	55
3	72F	I	W	50	15	65
4	58M	I	W	45	20	65
5	52M	AS	105	55	15	60

* Values in parentheses indicate normal range.
AB = advanced A-H block; AS = anteroseptal; I = inferior; IP = inferoposterior; MI = myocardial infarction; W = type I Wenckebach A-H block.

block was diagnosed according to the criteria of the New York Heart Association.[10]

Catheter technique: Intracardiac recordings were performed coincidental with the placement of pacemaker catheter electrodes for clinical indications in the coronary care unit at Jackson Memorial Hospital. In our institution, the documented appearance of a "complete" right bundle branch block pattern during acute transmural myocardial infarction is considered an indication for prophylactic transvenous demand pacing, even in the absence of manifest atrioventricular (A-V) conduction disturbances.[11] The procedure was explained to the patient and his or her relatives, and written informed consent was obtained. (Additional charges were not made for the recording of intracavitary electrograms, which were therefore performed without cost to the patient.)

A tripolar catheter with proximal electrodes spaced 10 mm apart and distal electrodes 1 mm apart was introduced percutaneously through the right femoral vein using image-amplified fluoroscopy. It was temporarily positioned across the septal leaflet of the tricuspid valve to obtain a His bundle electrograms from the electrode pair separated by 10 mm. No attempts were made to pace the atria or the His bundle during this part of the procedure. The catheter was then advanced into the right ventricular apex to record, first, a nonfiltered unipolar electrocardiogram from the tip electrode and, second, a filtered bipolar electrogram from this endocardial site using the distal electrode pair separated by 1 mm.[2–5] The position of the catheter electrodes at the right ventricular apex was confirmed fluoroscopically, as well as by the characteristics of the intracardiac unipolar electrogram and of the electrically or mechanically induced QRS complexes (abnormal superior and leftward axis orientation and negative deflections in lead V_1). Radiotransparent gold electrodes (Concept, Inc., Clearwater, Florida) were used to record the chest unipolar lead V_1 electrocardiogram in six patients. Bipolar electrograms from the septal A-V region and right ventricular apex, filtered 40 to 500 hertz and 400 to 500 hertz, respectively, were alternatively displayed together with three surface leads (I, II and V_1) on a multichannel photographic recorder (Electronics for Medicine DR-8). Paper speed was 100 mm/sec. After completion of the procedure, the corresponding catheter terminals were connected to an external battery-operated demand pacemaker, and a portable posteroanterior X-ray film was obtained. Repeat filtered bipolar electrograms from the right ventricular apex were later recorded in some patients (Table II) provided that a similar electrical location of the electrodes could be corroborated by X-ray film as well as by the features of the intracardiac and body surface electrocardiograms.

Intervals: A vernier device with an accuracy of ±1 msec was used to measure intervals. Five measurements were then averaged and values rounded to the nearest 5 msec. The following intervals were analyzed (figures in parentheses indicate normal values in our laboratory):

A-H interval (55 to 120 msec), measured from onset of the atrial deflection to the beginning of the His deflection in the His bundle electrographic lead.[1–5]

H-V interval (35 to 55 msec), measured from beginning of the His deflection to the earliest onset of the QRS complex in the surface leads. The latter were used to achieve consistency in measurement because the His bundle electrographic lead

TABLE II

Group 2: Intervals Measured in Patients Manifesting a Pattern of "Complete" Right Bundle Branch Block

Case no.	Age (yr) & Sex	Site of MI	Intervals (msec)* A-H (55–120)	H-V (35–55)	V-RVA (5–30)	H-RVA (40–85)	Repeat V-RVA CRBBB Pattern Persisted	Repeat V-RVA CRBBB Pattern Resolved
6	58F	AS	140	55	55	110	60	. . .
7	41M	AL	120	65	65	135	70	. . .
8	78M	AS	95	60	50	110	. . .	. . .
9	77M	AL	130	90	80	170	75	. . .
10	82M	AS	110	60	50	110	55	. . .
11	61M	AS	105	55	55	110	55	. . .
12	36M	AS	110	55	60	115	60	. . .
13	69M	IP	95	60	65	125	. . .	5 (Narrow QRS)
14	72M	AS	85	65	65	130	. . .	5 (Narrow QRS)
15	65M	AL	80	55	65	120	. . .	15 (CLBBB)
16	67M	AL	115	60	50	110	. . .	5 (CLBBB)
17	55M	AS	110	70	55	125	. . .	10 (CLBBB)
18	32M	IP	105	70	55	125	. . .	15 (Narrow QRS)
Range	. . .	. . .	80–140	55–90	50–80	110–170	55–75	
Mean	. . .	. . .	107.7	63	59.2	122.6	. . .	

* Values in parentheses indicate normal range.
AL = anterolateral; CLBBB = "complete" left bundle branch block; CRBBB = "complete" right bundle branch block.

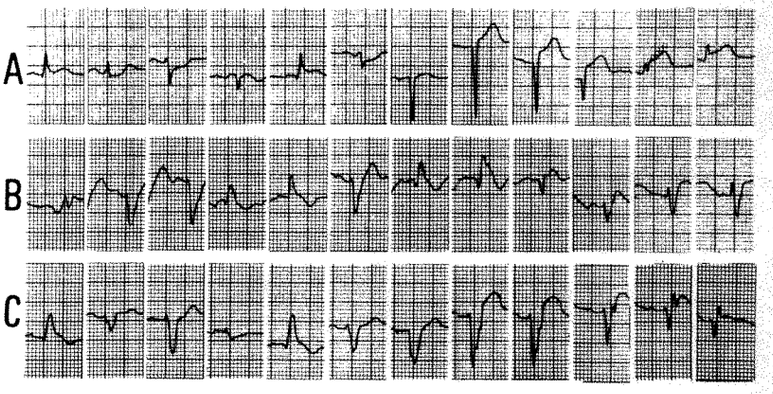


FIGURE 1. Case 17. Twelve lead electrocardiogram from a patient with acute anteroseptal myocardial infarction with narrow QRS complexes **(A)**, who later manifested wide ventricular complexes showing a "complete" right bundle branch block pattern **(B)**, as well as a "complete" left bundle branch block pattern **(C)**.

was not available for analysis when electrograms from the right ventricular apex were recorded.[1–5]

V-RVA interval (5 to 30 msec), measured from the beginning of the QRS complex in the surface leads to the onset of the filtered right ventricular apical electrogram.[1–5,9]

H-RVA interval (40 to 85 msec) was estimated by the sum of the separately measured H-V and V-RVA intervals.[1–5,9]

Results

Electrocardiographic data: *Group 1:* Two patients had an anteroseptal myocardial infarction, two an inferior infarction and one an inferoposterior myocardial infarction. All five patients had persistently narrow QRS complexes.

Group 2: Seven patients had an anteroseptal myocardial infarction, four an anterolateral myocardial infarction (Fig. 1 to 4) and two an inferoposterior myocardial infarction (Fig. 5 and 6). In all cases an electrocardiographic pattern of "complete" right bundle branch block occurred within 96 hours after admission. Although the two patients with an inferoposterior myocardial infarction had slurred S waves in leads I, aVL and V_6, leads V_1 and V_2 were not characteristic of "complete" right bundle branch block because they showed almost invisible or absent initial (small) r waves (Fig. 5). In six patients the "complete" right bundle branch block pattern disappeared while they were still in the unit. When this occurred the electrocardiogram showed narrow QRS complexes in three patients (Fig. 4 and 6) and a "complete" left bundle branch block pattern in the other three patients (Fig. 2).

Electrophysiologic data: *Group 1:* The A-H interval was normal in one patient and prolonged in another (Table I). The remaining three patients had second degree (Wenckebach type) or "advanced" atrioventricular block occurring between the A and H deflections. The H-V, H-RVA and V-RVA intervals were normal in all patients.

Group 2: The A-H interval was normal in 11 of 13 patients (range 80 to 140 msec, mean: 107.7 msec) (Table II). The H-V interval was at the upper limits of normal or prolonged in all 13 patients (range 55 to 90 msec, mean 63 msec) (Fig. 2, 3 and 6). The V-RVA in-

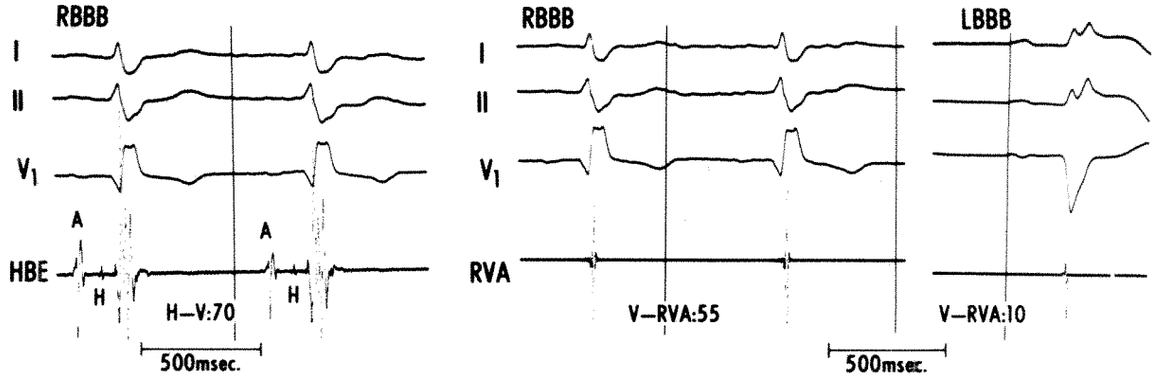


FIGURE 2. Case 17. His bundle (H) electrograms and right ventricular apical (RVA) electrograms from the same patient as in Figure 1. The H-V and V-RVA intervals were prolonged (70 and 55 msec, respectively) when the wide QRS complexes displayed a "complete" right bundle branch block (RBBB) pattern **(left panel)**. In contrast, the V-RVA interval was of normal duration (10 msec) when the wide ventricular complexes showed a "complete" left bundle branch block (LBBB) pattern **(right panel)**. A = atrial deflection recorded by the His bundle electrographic (HBE) lead. In this and all subsequent figures, values are expressed in msec.

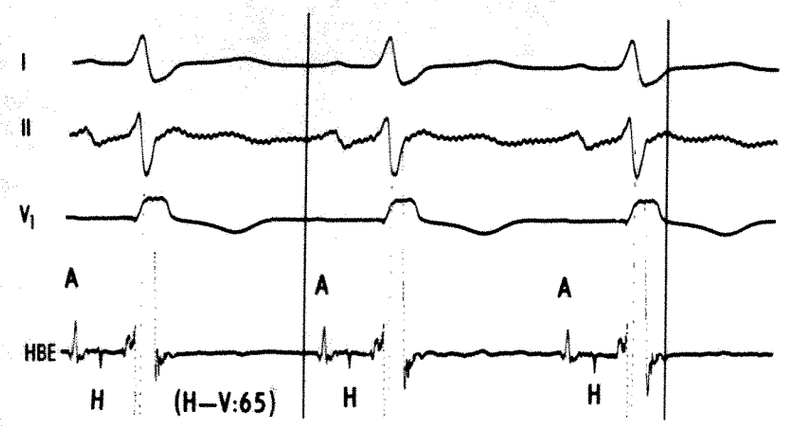


FIGURE 3. Case 14. His bundle electrograms from a patient with acute anteroseptal myocardial infarction. The H-V interval was prolonged (65 msec) when the QRS complexes were wide and displayed a "complete" right bundle branch block pattern. Intervals between vertical lines = 1,000 msec. Abbreviations as in Figure 2.

terval was prolonged in all 13 patients (range 50 to 80 msec, mean 59.2 msec) (Fig. 2, 4 and 6). In addition, the H-RVA interval was prolonged (range 110 to 170 msec, mean 122.6 msec) (Fig. 2 to 4 and 6). In seven patients with a persistent "complete" right bundle branch block pattern, the duration of the repeat V-RVA interval was not significantly changed from the initial measurements. However, in the six patients in whom this pattern spontaneously resolved (three patients with narrow QRS complexes and three with a "complete" left bundle branch block pattern), the duration of the V-RVA intervals had become normal (Fig. 2, 4 and 6).

Mortality: *Group 1:* All five patients in this group survived and were transferred out of the coronary care unit with 1:1 A-V conduction and a normal P-R interval.

Group 2: Five patients manifested "advanced" A-V block, three of whom showed, before the occurrence of the A-V block, a rate-unrelated "complete" left bundle branch block pattern alternating with (or occurring after) the previous "complete" right bundle branch block pattern. Four of these five patients died in the unit (the three with bilateral bundle branch block and one with a "complete" right bundle branch block pattern and an H-V interval of 80 msec). Two of the remaining eight patients died. In all, 6 of 13 patients in Group 2 died in the coronary care unit. All deaths were due to pump failure.

Discussion

The normal V-RVA interval: Previous studies have shown that, in patients with narrow QRS complexes and normal His-Purkinje conduction time, the His-right ventricular apex (H-RVA) interval gives an estimate of conduction time through the His bundle, right bundle branch and that part of the ventricular muscle located between the site from which the impulse emerges from the right bundle branch and the apex of the right ventricle.[2] On the other hand, the H-V interval is a measure of the conduction time from His bundle to the onset of ventricular depolarization, wherever and by whichever route or routes it occurs. The V-RVA interval does not represent conduction time from a specific ventricular site to the apex of the right ventricle, but simply reflects the elapsed time between the beginning of ventricular depolarization and activation of the right ventricular apex.[2]

Prolonged V-RVA interval in patients with a "complete" right bundle branch block pattern not

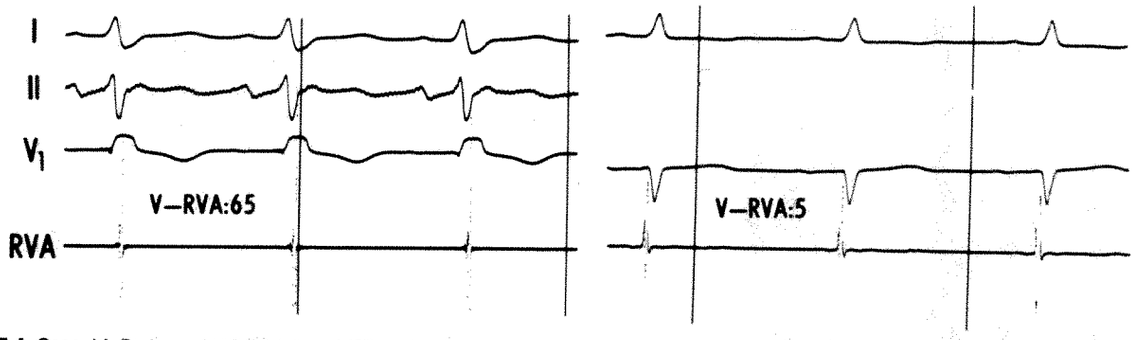


FIGURE 4. Case 14. Prolonged V-RVA interval (65 msec) recorded in the same patient as in Figure 3 when the wide ventricular complexes showed a complete right bundle branch block pattern **(left panel).** In contrast, the V-RVA interval had a normal duration (5 msec) when, subsequently, the QRS complexes became narrow **(right panel).** Intervals between vertical lines = 1,000 msec. Abbreviations as in Figure 2.

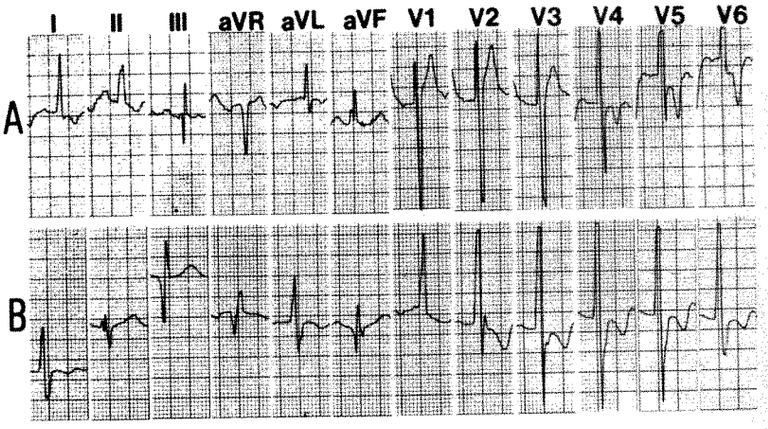


FIGURE 5. Case 13. Twelve lead electrocardiograms recorded before **(A)** and after **(B)** inferoposterior myocardial infarction. In **B** there was increased duration of the ventricular complexes with wide (terminal) deflections in leads I, aVL and the left chest leads. However, scalar leads V_1 and V_2 show tall R waves with almost invisible initial small (r) waves that made these ventricular complexes not characteristic of "complete" right bundle branch block.

due to myocardial infarction: When this pattern results from total conduction block in the main trunk of the right bundle branch, the H-RVA interval includes the conduction time from His bundle to the left septal surface (H-V interval) as well as that from the left septal surface to the recording electrodes (V-RVA interval). Several studies have reported prolonged V-RVA and H-RVA intervals in some patients with a "complete" right bundle branch block pattern resulting from primary conduction system disease or aberration of supraventricular impulses.[1,2,6,9,12] Concomitantly recorded H-V intervals have been normal or prolonged, the latter indicating the existence of an associated conduction delay in the left bundle branch or within the His bundle itself.

The normal V-RVA interval in patients with a "complete" right bundle branch block pattern: The reverse of this situation, namely, a "complete" right bundle branch block pattern coexisting with *normal* V-RVA and *normal* H-V and H-RVA intervals, has been considered to indicate that the conduction disturbance occurs beyond the main trunk of the right bundle branch,[4,8,13–15] distally at the level of the moderator band or terminally at the level of the Purkinje fibers,[8] or both. The latter conduction disturbances have been reported in some patients with atrial septal defect or after open heart surgery performed to correct certain congenital intracardiac malformations.[4,8,13–15] A normal V-RVA interval can be seen in some patients with conduction disturbances within the main trunk of the right bundle branch. Yet, for this to occur the H-RVA interval, although prolonged, should be only slightly longer than the (also prolonged) H-V interval (which reflects an associated conduction delay through the left bundle branch). But this type of partial bilateral bundle branch block would result in an "incomplete" (not "complete") right bundle branch block configuration in the surface leads.

The prolonged V-RVA interval in patients with a "complete" right bundle branch block pattern due to acute myocardial infarction: The studies mentioned suggest that the prolongation of the V-RVA and H-RVA intervals observed in 13 of 13 patients who manifested a "complete" right bundle branch block

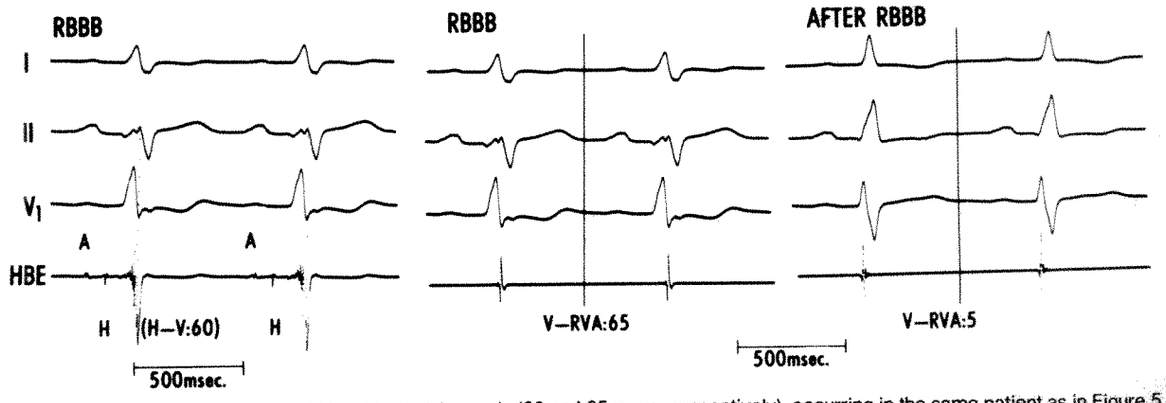


FIGURE 6. Case 13. Prolongation of the H-V and V-RVA intervals (60 and 65 msec, respectively), occurring in the same patient as in Figure 5 when the QRS complexes were wide and had predominantly positive deflections in leads V_1 and V_2 **(left** and **center panels).** In contrast, the V-RVA interval had a normal duration (5 msec) subsequently when the ventricular complexes became narrow **(right panel).** Abbreviations as in Figure 2.

pattern early in the course of acute transmural myocardial infarction reflected the existence of a conduction disturbance in the main trunk of the right bundle branch. This assumption is supported by the normal V-RVA intervals recorded in the five patients with persistently narrow QRS complexes and in the six patients whose "complete" right bundle branch block pattern disappeared.

Because of the constraints imposed by the clinical setting in which the intracardiac electrograms were obtained (acute myocardial infarction), and because the recordings were obtained during catheter insertion for therapeutic reasons, additional maneuvers, such as catheter manipulations to record right bundle potentials or His bundle pacing, were not performed. Therefore, in our patients we were not able to repeat the studies of Narula[16] and El Sherif et al.,[17] who observed that His bundle pacing could normalize (therefore decreasing the QRS duration) some chronic "complete" bundle branch block patterns. These authors considered that the latter could be due to a lesion, or lesions, occurring within the His bundle itself (not necessarily located in the trunk of the right bundle branch). An intra-Hisian conduction disturbance capable of producing a "complete" right bundle branch block pattern can cause a prolongation of the H-RVA and V-RVA intervals, as when the main trunk of the right bundle branch is affected. In our patients with acute myocardial infarction and prolonged V-RVA intervals, the coexistence of a prolonged H-V interval, or one at the upper limit of normal, is in keeping with previous data,[16,17] but might also reflect the large incidence of multilevel block that can occur in patients with anterior myocardial infarction and wide QRS complexes.

Electrophysiologic implications: The newer techniques of obtaining intracardiac electrograms (use of close bipolar leads and filters and methods of recording the electrical activity of the proximal portions of the intraventricular conduction system and other selected endocardial or epicardial sites) have enhanced our knowledge of several types of intraventricular conduction defects that occur in the human heart. The present study extends the usefulness of these techniques to conduction defects occurring in patients with acute transmural myocardial infarction. For example, a normal V-RVA interval was recorded in the eight patients with persistently or intermittently narrow QRS complexes. It appeared, therefore, that transmural myocardial infarction in itself did not produce a lengthening of the V-RVA interval, even when the interventricular septum was involved.

Moreover, the V-RVA interval can be of help in the categorization of patients who have an inferoposterior myocardial infarction pattern, prolonged intraventricular conduction time and predominantly positive QRS deflections in scalar leads V_1 and V_2. When the infarction pattern results from coronary disease (true myocardial infarction) and a normal (or prolonged) P-R interval coexists with prolonged V-RVA and prolonged H-RVA intervals, the conduction disturbance occurs in the right bundle branch and perhaps within the His bundle itself. On the other hand, a pseudoinfarction pattern due to ventricular preexcitation (in patients without coronary artery disease) resulting from left-sided accessory pathways is characterized (when fusion QRS complexes are present) by a normal P-R interval, a prolonged V-RVA interval and a normal H-RVA interval if the accessory pathway is of the Mahaim type[18] and by a short P-R interval, prolonged V-RVA interval and normal H-RVA interval if the accessory pathway is of the Kent type.[3]

Future studies should be oriented toward the corroboration of these assumptions, as well as to the determination of whether *left* ventricular apical electrograms can differentiate between the wide QRS complexes produced by a block in the main trunk of the left bundle branch and those resulting from distal, peripheral or parietal left ventricular conduction disturbances.

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Regional Myocardial Function at Rest and After Rapid Ventricular Pacing in Patients After Myocardial Revascularization by Coronary Bypass Graft or by Collateral Vessels

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The relation between the anatomy of the left anterior descending coronary artery and regional myocardial function was studied at rest and after rapid ventricular pacing in 194 patients with proximal disease of this artery. Sixty patients were restudied 4 months after coronary bypass surgery. All of these patients had a graft to the left anterior descending coronary artery after operation. Twenty-two persons with normal coronary arteriograms served as control subjects. Coronary obstruction was measured with quantitative coronary arteriography and was classified as critical stenosis (75 to 99 percent luminal narrowing) or occlusion (100 percent). Regional wall motion was defined by hemiaxis shortening. Four groups were established: group A, obstruction without revascularization; group B, obstruction with revascularization by collateral vessels; group C, obstruction with revascularization by a patent graft; group D, obstruction with revascularization by a stenosed or occluded graft. At rest, regional motion diminished in group A with critical stenosis and further with occlusion (from 39 to 25 percent and to 5 percent, $P < 0.001$, $P < 0.001$); in group B, with critical stenosis (from 39 to 24 percent, $P < 0.001$) but not with occlusion (from 24 to 19 percent, $P > 0.05$). In contrast, in group C motion remained unchanged (from 39 to 31 percent and to 32 percent, $P > 0.05$, $P > 0.05$). After pacing, regional motion became akinetic in groups A and B with critical stenosis and remained unchanged with occlusion. In contrast, in group C wall motion remained normal after pacing with critical stenosis and with occlusion. Results in group D were comparable with those in group B. Ejection fraction showed parallel and left ventricular end-diastolic pressure inverse changes as compared with regional motion.

When coronary stenosis progresses to occlusion without revascularization, myocardial contractility becomes depressed at rest and after pacing. Revascularization by collateral vessels preserves resting function in coronary occlusion to some extent but is ineffective after pacing. Successful surgical revascularization prevents loss of function at rest and after pacing in critical stenosis and in occlusion.

Revascularization of myocardium supplied by an obstructed or occluded artery can be achieved by coronary collateral vessels or an aortocoronary bypass graft. Although controversy exists over the significance of collateral vessels in preserving myocardial function,[1–4] several studies[5–7] have demonstrated improvement in left ventricular contractility after surgical revascularization. However, some investigators[8–10] found no significant improvement in ejection fraction at rest after successful surgical revascularization. In patients with chronic stable angina ischemia is usually absent at rest but develops during stress because of a disparity between the amount of oxygen delivered to the myocardium

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by the coronary blood supply and the requirements of cardiac muscle in the postobstructive area. Ischemia in these patients is evidenced by stress-induced reversible cardiac failure and reversible asynergy.[11,12] Because ischemia in chronic coronary artery disease in the stable state is present during stress only, augmentation of myocardial function after aortocoronary bypass surgery can be demonstrated during stress but not at rest.

The purpose of this study is (1) to define the effects of pacing stress on left ventricular function with different degrees of coronary obstruction, and (2) to compare the effects of myocardial revascularization by collateral vessels or a coronary artery bypass graft with different degrees of coronary obstruction at rest and during stress.

Methods

Patients

Data on 334 consecutive patients (8 women and 326 men between 27 and 65 years of age) with obstructive coronary artery disease were analyzed. We excluded 140 patients because of one or more of the following features: (1) significant (greater than 50 percent luminal narrowing) obstruction of the first marginal branch of the left circumflex artery (74 patients), (2) significant disease of the left main coronary artery (7 patients), (3) no disease of the left anterior descending coronary artery (42 patients), (4) peripheral disease of the left anterior descending coronary artery (8 patients), (5) atrial fibrillation at the time of study (2 patients), and (6) technically poor angiograms (28 patients). The remaining 194 patients had significant proximal obstruction of the left anterior descending coronary artery. Any collateral supply evident in the cineangiograms was carefully noted.

Criteria for the presence of coronary collateral vessels, either intra- or intercoronary anastomosis, required visualization of the vessel segment distal to the obstruction. These criteria are similar to those of Hamby et al.[3] According to these criteria the collateral supply to the left anterior descending coronary artery was present in 72 and absent in 122 patients. Additional significant disease of the right coronary artery was found in 61 patients and additional disease of the left circumflex artery distal to the origin of the first left marginal branch in 24 patients. A typical history and electrocardiographic changes (pathologic Q waves) suggestive of old myocardial infarction (75 anterior, 22 inferior) were present in 97 patients.

Sixty patients could be restudied between 3 and 6 months (mean 4.3 months) after aortocoronary bypass surgery. The indication for surgery was stable angina in 58 patients and unstable angina in 2. The patients had ventriculographic and coronary arteriographic studies within 6 weeks before operation. No patient operated on and restudied had an acute event between the catheterization study and operation. Twenty-seven patients had one graft, 24 patients had two grafts and 9 patients had three grafts. A graft to the left anterior descending coronary artery was performed in each patient. Two patients had perioperative myocardial infarction as judged by new Q waves and serum enzyme levels. Twenty-two patients studied because of chest pain but found to have normal coronary arteriograms and a normal left ventriculogram served as control subjects.

Catheterization Study

All patients were studied during normal sinus rhythm. No patient experienced chest pain during catheterization except after pacing stress. No premedication was used. Nitrates and beta adrenergic blocking agents were discontinued at least 3 days before study. Left heart catheterization was performed by the retrograde technique. After measurement of left ventricular systolic and end-diastolic pressures monoplane angiography was performed in the 30° right anterior oblique projection with injection of 50 ml of Urografin-7®. Thereafter, coronary arteriography was carried out using the Judkins technique[13] with 35 mm film taken at 32 or 48 frames/sec utilizing the Philips dual field 9 and 5 inch image intensifier system. Selective coronary injections were made manually using multiple projections.

A pacing test was performed in 82 patients. A bipolar electrode was placed into the right ventricle. Thirty minutes after the last angiogram right ventricular pacing was started at a rate of 110 beats/min and was gradually increased under left ventricular pressure recording to a rate of 170 beats/min. Pacing rate was kept constant for 1 minute. After pacing was stopped, left ventricular systolic and end-diastolic pressures were recorded for 30 seconds. After a pause of 10 to 15 minutes pacing was repeated and a second ventriculogram was obtained immediately after pacing was stopped.

From the cineangiographic frames silhouettes of the left ventricular cavity were drawn at end-diastole and end-systole. Extrasystolic and postextrasystolic cycles were not analyzed. The ejection fraction was calculated using the monoplane area-length method.[14] Segmental wall motion was measured from the end-diastolic and end-systolic outlines of the left ventricle (Fig. 1). The long axis (L) was divided into four equal parts, and three perpendicular lines were constructed. Each hemiaxis (from the long axis to the endocardial surface) was measured and the percent shortening was calculated as end-diastolic minus end-systolic divided by end-diastolic hemiaxis multiplied by 100 percent. The individual values of hemiaxes and R_2 and R_3 and of the long axis (L) were averaged to get a representative measurement of segmental wall motion of the area of myocardial territory of the left anterior descending coronary artery.[15]

The degree of coronary stenosis was measured using the technique of quantitative coronary arteriography as suggested by Brown et al.[16] Coronary lesions were traced from two perpendicular projected 35 mm cineangiographic views. Magni-

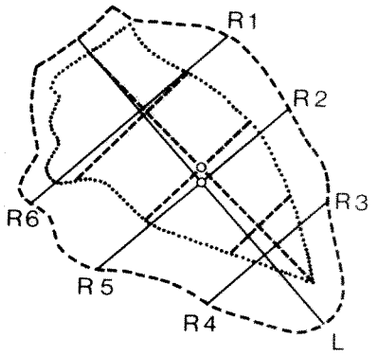


FIGURE 1. End-diastolic (**dashed border**) and end-systolic (**dotted border**) ventriculographic silhouettes of the left ventricle. The long axis (L) for end-diastole (**solid line**) and end-systole (**dashed line**) is depicted. The **open circles** represent the "mid point" of each silhouette. The percent shortening of each hemiaxis (R_1 to R_6) is calculated as the end-diastolic minus the end-systolic hemiaxis divided by the end-diastolic hemiaxis times 100 percent. The anterior wall is marked by the shaded area. The area perfused by the left anterior descending coronary artery was taken as the average of $R_2 + R_3 + L$.

fication and distortion were corrected using the coronary catheter. The technique assumes an elliptical lumen of the vessel and calculates the percent of reduction in luminal area in the stenosis. Diameters of the vessel were measured from end-diastolic frames. The normal lumen is calculated as the average of the normal lumen proximal and distal to the stenosis. Two determinations of 14 stenoses by the same trained observer showed an average difference of 1.8 ± 2.0 percent stenosis (mean ± standard deviation). One determination of two trained observers (18 stenoses) showed an average difference of 2.8 ± 1.6 percent stenosis.

Patients were operated on using total cardiopulmonary bypass and a disposable bubble oxygenator. Cardioplegic arrest and hypothermia were used for distal coronary anastomoses. The proximal aortic anastomoses were performed in the beating heart with the aid of a partially occluding aortic clamp.

For statistical comparison the paired or unpaired *t* test was used.

Results

Patients were classified into four groups according to the anatomy of the left anterior descending coronary artery: group A, "pure" obstruction without revascularization by collaterals or by graft (105 patients); group B, obstruction with spontaneous revascularization by angiographically visible collateral supply to the post-obstructive vessel segment (72 patients); group C, obstruction with successful surgical revascularization (41 patients); and group D, obstruction with unsuccessful surgical revascularization (graft failure) (19 patients).

Effect of "pure" stenosis on left ventricular function at rest and during stress (group A): Data on regional wall motion related to the degree of stenosis of the left anterior descending coronary artery are presented in Figure 2 and Table I. With less than 75 percent stenosis, wall motion remained normal at rest and unchanged after pacing. With 75 to 99 percent stenosis, wall motion began to diminish at rest ($P < 0.001$ when compared with prior stenosis). Pacing produced a significant further reduction in wall motion with this degree of stenosis ($P < 0.001$). With complete vessel occlusion, wall motion was nearly absent at rest and remained unchanged after pacing ($P > 0.05$). There

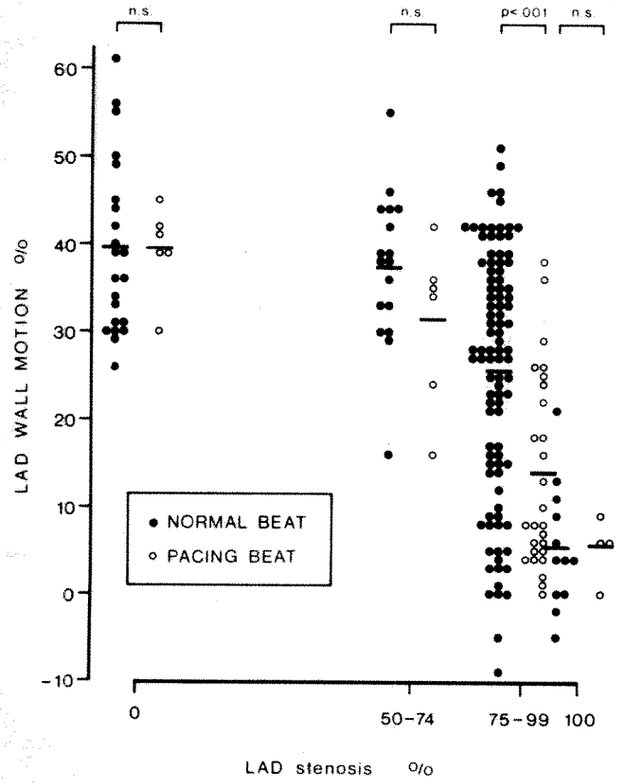


FIGURE 2. Group A (obstruction without revascularization). Individual data on wall motion of the area perfused by the left anterior descending coronary artery (LAD) are correlated with the degree of stenosis during a normal beat (**closed circles**) and during a pacing beat (**open circles**). Four degrees of stenosis are indicated: 0 percent (control), 50 to 74 percent, 75 to 99 percent and 100 percent. Wall motion diminishes at rest in patients with 75 to 99 percent stenosis and is further depressed during pacing. In patients with 100 percent occlusion akinesia develops both at rest and during pacing. The **solid horizontal lines** in each column indicate mean values. n.s. = not significant; p = probability.

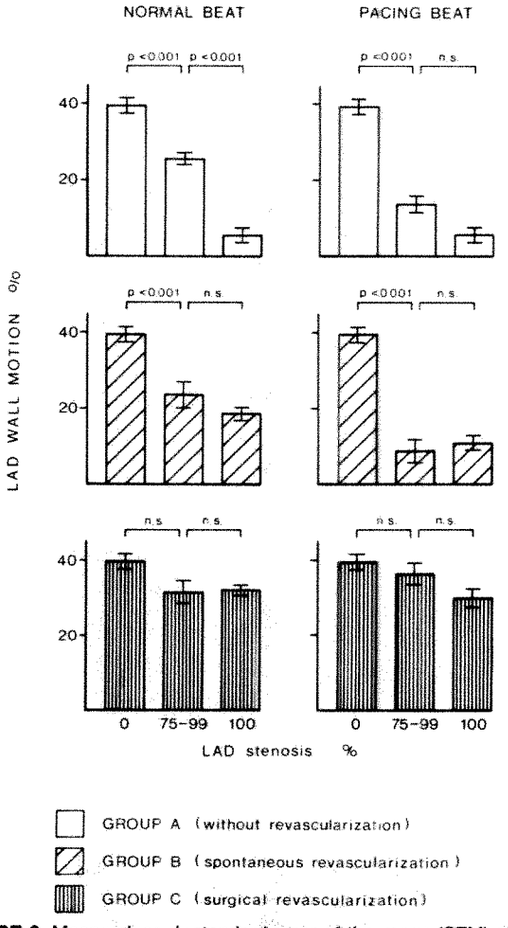


FIGURE 3. Mean values ± standard error of the mean (SEM) of wall motion of the area perfused by the left anterior descending coronary artery (LAD) for 0 percent, 75 to 99 percent and 100 percent stenosis. Data are shown during a normal beat and during a pacing beat for patients in groups A, B and C. LAD stenosis 0 percent represents the control group. Abbreviations as in Figure 2.

were 17 patients with 50 to 74 percent stenosis. Because none of these patients were restudied after aortocoronary bypass surgery, data on patients with this degree of severity of stenosis are presented only in Figure 2 and are not included in the following results.

Effect of revascularization on the relation between coronary stenosis and left ventricular function (groups A, B and C): Figure 3 illustrates regional wall motion for groups A, B and C according to the degree of stenosis of the left anterior descending coronary artery. In group A (without revascularization) during a normal beat a stepwise reduction of motion was observed when stenosis progressed from 0 to 75 to 99 percent and from 75 to 99 percent to complete occlusion. In group B (spontaneous revascularization) a significant decrease in wall motion was seen between 0 and 75 to 99 percent stenosis but no further depression with complete occlusion. In group C (surgical revascularization) no reduction in wall motion was seen with progression of stenosis to complete occlusion.

During pacing, groups A and B revealed a steep decrease in regional motion with 75 to 99 percent stenosis

TABLE I

Wall Motion of the Area Supplied by the Left Anterior Descending Coronary Artery at Rest and After Pacing (%) in Groups A to D

Normal Beat

Degree of LAD Stenosis	Group A	Group B	Group C	Group D
0 percent (control) Mean ± SEM	39.4 2.1 (no. = 22)			
75–99% Mean ± SEM	25.4 1.5 (no. = 93)	23.6 3.5 (no. = 11)	31.4 3.1 (no. = 7)	29.4 4.3 (no. = 5)
100% Mean ± SEM	5.4 2.1 (no. = 12)	18.8 1.7 (no. = 61)	31.9 1.5 (no. = 34)	22.0 3.1 (no. = 14)

Statistical Comparisons Between Groups (*P* Value)

	A/B	A/C	A/D	B/C	B/D	C/D
75–99%	NS	NS	NS	NS	NS	NS
100%	†	†	†	†	NS	†

Pacing Beat

Degree of LAD Stenosis	Group A	Group B	Group C	Group D
0% (control) Mean ± SEM	39.3 2.1 (no. = 6)			
75–99% Mean ± SEM	13.7 2.1 (no. = 27)	8.7 2.9 (no. = 6)	36.2 2.9 (no. = 5)	16.0 6.5 (no. = 3)
100% Mean ± SEM	5.8 1.9 (no. = 4)	10.8 2.2 (no. = 10)	29.9 2.6 (no. = 18)	8.7 3.5 (no. = 3)

Statistical Comparison Between Groups (*P* value)

	A/B	A/C	A/D	B/C	B/D	C/D
75–99%	NS	‡	NS	‡	NS	*
100%	NS	‡	NS	‡	NS	†

* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.001$.
Group A = obstruction without revascularization; group B = obstruction with spontaneous revascularization; group C = obstruction with successful surgical revascularization; group D = obstruction with unsuccessful surgical revascularization (graft failure).
LAD = left anterior descending coronary artery; NS = not significant; *P* = probability value; SEM = standard error of the mean.

and no further depression with complete occlusion (Fig. 3). In contrast, in group C, regional wall motion remained unchanged with increasing degrees of stenosis. Table II contains additional data on heart rate, left ventricular systolic and end-diastolic pressures and ejection fraction in each subset of patients with isolated disease of the left anterior descending coronary artery. Changes in ejection fraction are parallel with changes in segmental wall motion in groups A, B and C. At rest a stepwise decrease was seen in group A (P <0.001 and, P <0.001, respectively). In group B a significant decrease in ejection fraction was observed only between 0 and 75 to 99 percent stenosis but no further decrease with complete occlusion (P <0.05 and P >0.05, respectively). In group C no depression of ejection fraction was seen with increasing degrees of stenosis (P >0.05 and P >0.05, respectively).

During pacing a steep decrease in ejection fraction was found in group A, and in group B when stenosis reached to 75 to 99 percent (P <0.001); no further

TABLE II

General Hemodynamics

Normal Beat

Degree of LAD Stenosis	Group A HR	LVSP	LVEDP	EF	Group B HR	LVSP	LVEDP	EF	Group C HR	LVSP	LVEDP	EF	Group D HR	LVSP	LVEDP	EF
0% (control)																
Mean	74.6	130	12.6	68.9												
± SEM	3.3	3	0.8	1.8												
	(no. = 22)															
75–99%																
Mean	78.0	131	21.9	53.5	75.0	139	20.9	60.5	79.3	138	10.0	69.2	81.8	140	15.0	56.0
± SEM	2.9	4	1.7	2.4	3.0	5	1.8	2.7	3.9	5	2.2	1.1	8.7	9	5.0	6.4
	(no. = 33)				(no. = 8)				(no. = 6)				(no. = 4)			
100%																
Mean	81.1	127	17.2	40.3	74.2	135	16.3	53.0	84.2	149	13.4	66.6	83.0	150	18.0	53.7
± SEM	4.3	8	2.6	3.5	2.4	5	1.5	2.0	3.5	5	1.4	2.7	4.6	11	1.8	5.9
	(no. = 7)				(no. = 30)				(no. = 12)				(no. = 7)			

Statistical Comparisons Between Groups (P value)

	A versus B				A versus C				A versus D				B versus C				B versus D				C versus D			
	HR	SP	EP	EF	HR	SP	EP	EF	HR	SP	EP	EF	HR	SP	EP	EF	HR	SP	EP	EF	HR	SP	EP	EF
75–99%	NS	NS	NS	NS	NS	NS	†	‡	NS	NS	NS	NS	NS	NS	†	*	NS	NS	NS	NS	NS	NS	NS	NS
100%	NS	NS	NS	*	NS	*	NS	‡	NS	NS	NS	NS	*	NS	NS	‡	NS	NS	NS	NS	NS	NS	NS	*

Pacing Beat

Degree of LAD Stenosis	Group A HR	LVSP	LVEDP	EF	Group B HR	LVSP	LVEDP	EF	Group C HR	LVSP	LVEDP	EF	Group D HR	LVSP	LVEDP	EF
0%																
Mean	85.2	137	14.3	70.8												
± SEM	4.9	12	1.5	1.6												
	(no. = 6)															
75–99%																
Mean	73.4	148	31.7	44.4	78.8	139	31.4	40.8	79.8	134	11.6	70.0	§	§	§	§
± SEM	3.6	11	2.1	3.7	4.0	18	1.4	5.2	2.5	6	2.3	2.0				
	(no. = 7)				(no. = 6)				(no. = 5)							
100%																
Mean	67.5	135	30.5	36.5	86.3	133	34.0	37.4	84.1	144	19.1	62.9	§	§	§	§
± SEM	4.4	10	1.9	5.8	6.9	6	3.4	4.1	4.3	6	1.4	2.3				
	(no. = 4)				(no. = 8)				(no. = 17)							

Statistical Comparisons Between Groups (P value)

	A versus B				A versus C				A versus D				B versus C				B Versus D				C versus D			
	HR	SP	EP	EF	HR	SP	EP	EF	HR	SP	EP	EF	HR	SP	EP	EF	HR	SP	EP	EF	HR	SP	EP	EF
75–99%	NS	NS	NS	NS	NS	NS	‡	‡	...	...	...	...	NS	NS	‡	‡	...	...	...		...	...	...	...
100%	NS	NS	NS	NS	NS	NS	‡	‡	...	...	...	...	NS	NS	‡	‡	...	...	...	...	...	...	...	...

* P <0.05.
† P <0.01.
‡ P <0.001.
§ Number of observations did not permit statistical comparison.
Groups A to D as defined in Table I.
EF = ejection fraction (%); EP, LVEDP = left ventricular end-diastolic pressure (mm Hg); HR = heart rate (beats/min); LAD = left anterior descending coronary artery; LVSP, SP = left ventricular systolic pressure (mm Hg); no. = number of subjects; NS = not significant; P = probability; SEM = standard error of the mean.

change occurred with occlusion ($P > 0.05$). In contrast, patients in group C showed no change in ejection fraction with progression of obstruction ($P > 0.05$ and $P > 0.05$, respectively). Left ventricular end-diastolic pressure increased at rest and after pacing in groups A and B when stenosis reached 75 to 99 percent ($P < 0.001$) and remained elevated in complete occlusion. In group C no change in end-diastolic pressure occurred with progression of stenosis ($P > 0.05$). Heart rate and left ventricular systolic pressure were comparable in the three groups ($P > 0.05$) at rest and after pacing (Table II).

Comparisons among different types of revascularization at rest and after pacing (groups B, C and D): Figure 4 presents individual data on regional wall motion in groups B, C and D with 75 to 99 percent stenosis and with complete occlusion and compares them with data in group A. With 75 to 99 percent stenosis, wall motion at rest was similar in all four groups. With complete occlusion, wall motion was greater in groups B, C and D than in group A. Regional motion in group C was also significantly greater than in groups B ($P < 0.001$) and D ($P < 0.01$).

During pacing, with 75 to 99 percent stenosis regional motion was similar in groups B and D but augmented in group C as compared with group A (Fig. 4). Furthermore, group C showed greater regional motion than groups B ($P < 0.001$) and D ($P < 0.05$). With complete occlusion during pacing, wall motion was similar in groups B and D but increased in group C compared with group A. Wall motion in group C was again greater than in groups B ($P < 0.001$) and D ($P < 0.01$). Figure 5 shows ventricular silhouettes of a patient in group A with 95 percent stenosis of the left anterior descending coronary artery: Wall motion was normal at rest but severely depressed during pacing stress. After successful bypass grafting, wall motion was normal at rest and during stress. Thus, the ischemic response was abolished after coronary bypass surgery.

Differences in ejection fraction were generally similar to differences in regional wall motion when only cases of isolated disease of the left anterior descending coronary artery were considered (Table II). Left ventricular end-diastolic pressure was elevated when systolic ejection fraction was depressed.

Heart rate and left ventricular systolic pressure were not different among groups except that heart rate in group C was higher than in group B with complete vessel occlusion ($P < 0.05$) and left ventricular systolic pressure was higher in group C than in group A with complete occlusion ($P < 0.05$). After pacing no significant difference was found among groups.

Graft patency rate was 89 percent (91 of 102 grafts) 4 months after operation. Five grafts to the left anterior descending coronary artery were occluded and nine

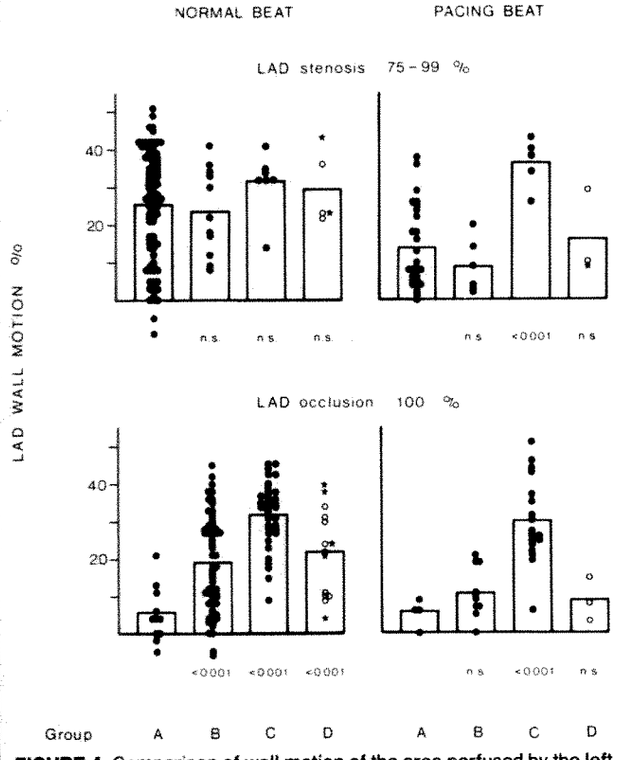


FIGURE 4. Comparison of wall motion of the area perfused by the left anterior descending coronary artery (LAD) among the four groups during the normal beat (**left**) and pacing beat (**right**). The **upper panels** show data in cases of stenosis of the native artery (75 to 99 percent luminal narrowing); the **lower panels** refer to data in cases of complete occlusion. Significant differences between group A (obstruction without revascularization) and groups B, C and D are shown below the columns. In group D, patients with a stenosed graft (**open circles**) and with an occluded graft (**stars**) are indicated. Abbreviations as in Figure 2.

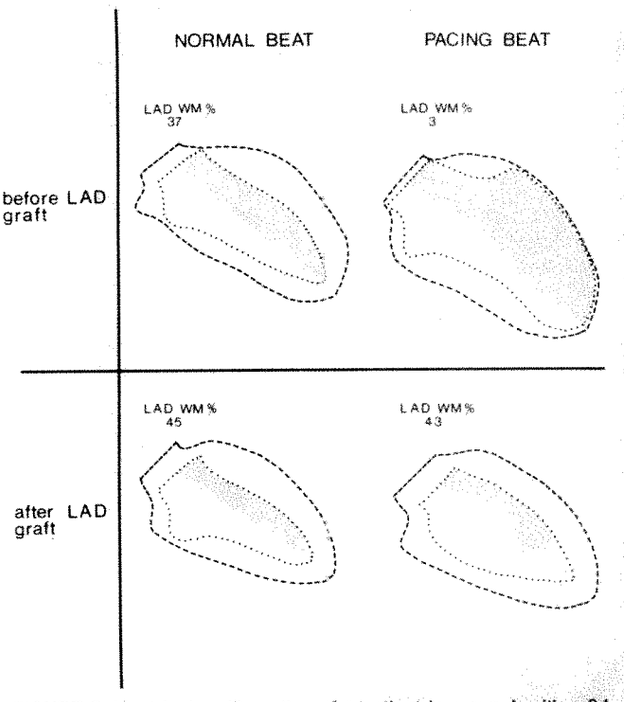


FIGURE 5. Ventricular silhouettes of a patient in group A with a 94 percent stenosis of the left anterior descending coronary artery (LAD). Anterior wall motion (WM) was normal at rest but became akinetic with pacing before bypass surgery. After the graft, wall motion is normal at rest and during pacing stress.

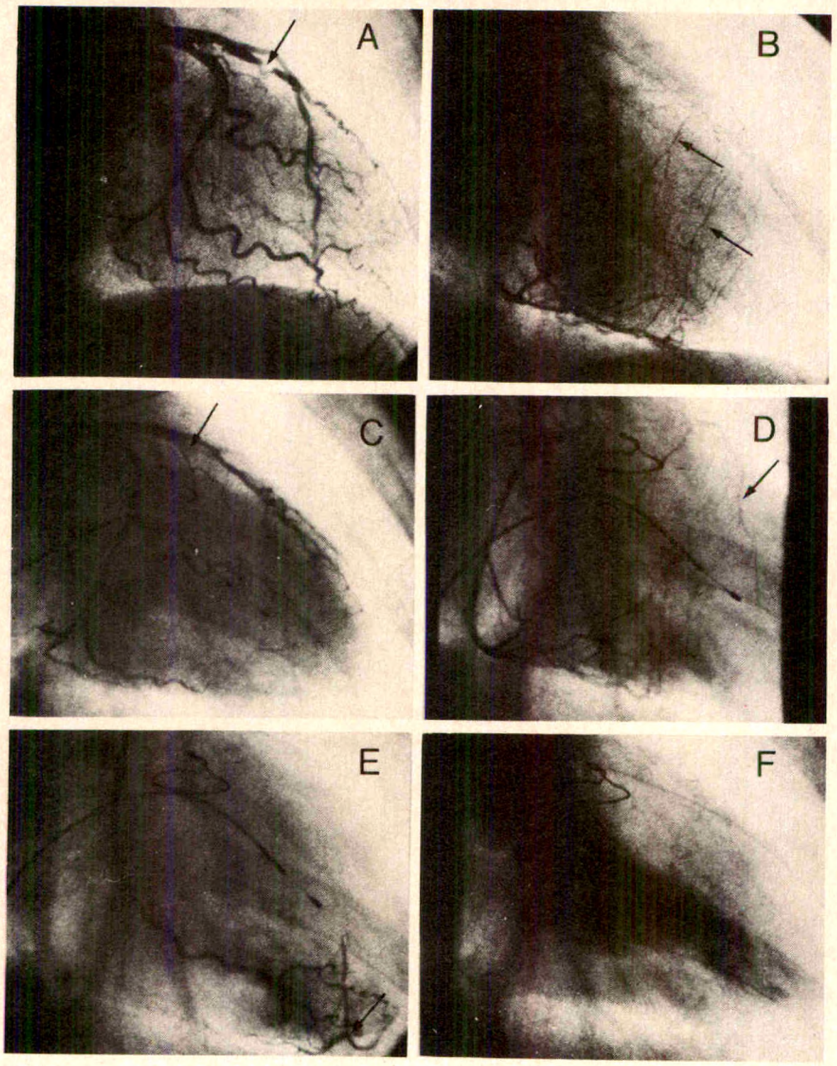


FIGURE 6. Pre- and postoperative coronary arteriograms of a patient in group D. **A,** preoperative left coronary injection. Severe proximal stenosis (**arrow**) of the left anterior descending coronary artery is present. **B,** preoperative right coronary injection. Collateral vessels to the left coronary system are seen within the septum (**arrows**). **C,** postoperative left coronary injection. Complete occlusion of the left anterior descending coronary artery is seen (**arrow**). **D,** postoperative right coronary injection. A rich collateral network within the septum fills the left anterior descending coronary artery (**arrow**). **E,** postoperative injection into a graft to the second marginal branch fills collateral vessels to the distal part of the left anterior descending coronary artery (**arrow**). **F,** postoperative end-systolic ventriculogram, normal beat. Only slight apical hypokinesia is seen. A protective effect of collateral supply to the left anterior descending coronary artery is documented in this case after graft occlusion (not depicted) associated with occlusion of the native artery.

grafts were obstructed (more than 75 percent luminal narrowing) at the proximal (two grafts) or distal anastomosis (seven grafts). In Figure 4, patients in group D with stenosed and occluded grafts are separated. With complete occlusion no difference in wall motion between these subsets was found at rest (20.1 ± 3.4 percent, no. = 9, versus 25.4 ± 6.5 percent, no. = 5, $P > 0.05$). When the graft was stenosed and the native artery occluded, the myocardium was perfused exclusively by the stenosed graft. When both the graft and the artery were occluded, collateral vessels supplied the perfusion area of the left anterior descending coronary artery in all cases (five of five cases). Figure 6 shows a typical example of this situation: A rich collateral supply to the left anterior descending coronary artery was seen after occlusion of the graft and native artery, and the effect of this spontaneous revascularization was documented by a well preserved wall motion of 38 percent.

Significance of "critical obstruction": After stress a diminution in wall motion was found before operation in patients with 75 to 99 percent stenosis (from 25 to 14 percent), with 75 to 99 percent stenosis associated with collateral vessels (from 24 to 9 percent, $P < 0.05$) and with complete occlusion associated with collateral vessels (from 19 to 11 percent, $P < 0.01$). Regional motion in these subsets was similar at rest and after pacing but was reduced in both instances from that of normal subjects ($P < 0.001$). Thus, these subsets can be defined as "critical obstruction"; that is, acute ischemic dysfunction occurs during stress while resting function is maintained. However, a certain degree of dysfunction was found in these patients even at rest. Therefore, we tried to determine if this moderate depression would be reversible after surgical revascularization. Segmental function was compared before and after successful graft surgery within the same patient (Fig. 7). At rest, wall motion increased from 27.1 to 32.7 percent ($P < 0.01$) and after stress from 10.4 to 35.2 percent ($P < 0.01$).

Discussion

Problems of study: It is difficult to evaluate the effects of therapeutic procedures on myocardial function in coronary artery disease because the extension of the disease is highly variable: The number of obstructions,

degree of obstruction, perfusion area of obstructed vessel and presence or absence of collateral vessels influence myocardial function in a complex manner. Therefore, we focused our investigation by (1) utilizing the technique of quantitative coronary angiography, which measures precisely the degree of obstruction; (2) limiting the data to the left anterior descending coronary artery, which has the least variable perfusion area of the vessels supplying the left ventricle[17]; and (3) classifying the stenotic lesions according to the presence or absence of coronary collateral supply. In addition to these modifications a pacing stress test was used to determine the functional significance of different degrees and types of obstruction and to define the effect of surgical revascularization on myocardial function. We expected that this approach would clarify the extent to which myocardial revascularization augments myocardial function.

The technique of quantitative coronary angiography measures luminal obstruction.[16] The technique assumes elliptical vessel cross section and calculates the percent of luminal narrowing from paired perpendicular angiographic views. Frames are selected at end-diastole. In our experience, with careful attention to filming technique, more than 95 percent of the lesions of the left anterior descending coronary artery can be measured. We measured only the percent of luminal narrowing, not the length of stenosis. We limited our study to only two grades of obstruction, 50 to 74 percent and 75 to 99 percent, thus reducing the likelihood of erroneous measurements.

Surgical revascularization: This study demonstrates that successful surgical revascularization preserves myocardial function as compared to "pure" coronary stenosis both during stress (when the native artery is critically stenosed or completely occluded) and at rest (when the native artery is occluded).

To evaluate the effect of coronary revascularization, we defined the relation between severity of stenosis and segmental wall motion in cases without revascularization. We found that with 75 to 99 percent coronary stenosis loss of wall function was moderate and that with 100 percent occlusion akinesia developed when revascularization was absent. With 75 to 99 percent stenosis further depression of wall motion occurred during pacing. This stress-induced asynergy documents that stenosis limited adequate blood supply during increased demand; that is, the stenosis was "critical." However, the stenosis was critical even at rest because wall motion was moderately reduced during the normal beat. The finding that after correction of severe stenosis wall motion was augmented at rest and during stress in patients with stable angina suggests that a stage of reversible asynergy is produced by critical coronary stenosis. Further progression of stenosis to complete occlusion induced irreversible asynergy. Whether progression of stenosis or repeated episodes of stress-induced asynergy, or both, precipitate irreversible loss of wall motion remains to be clarified.

It is well known that proximal coronary stenosis often progresses to complete occlusion after insertion of bypass graft.[18,19] In our series 53 percent of proximal native artery stenoses were found to be completely occluded after operation. The deleterious effect of vessel occlusion on myocardial function at rest and after pacing was prevented by a patent graft. Furthermore, regional function at rest and during stress was augmented after grafting a vessel with a critical obstruction. We conclude that a critical obstruction should be corrected with bypass graft because cardiac function improves thereafter. Our results apply only to an early restudy; deterioration of function may occur after several years because of changes in the native artery or graft anatomy.[20–22]

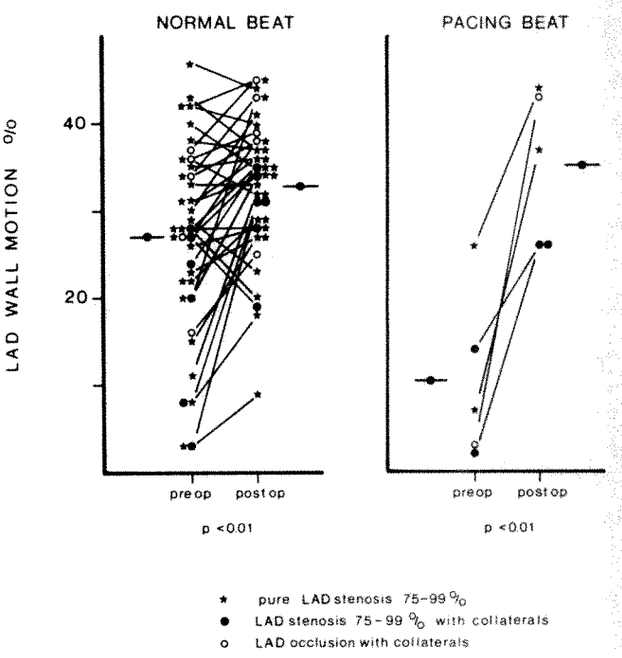


FIGURE 7. Wall motion of the area perfused by the left anterior descending coronary artery (LAD) in critical coronary obstruction ("pure" LAD stenosis), LAD stenosis with collateral vessels and LAD occlusion with collateral vessels before (preop) and after (postop) bypass surgery. A significant increase in wall motion occurred at rest (normal beat) and during pacing stress.

Revascularization by collateral vessels: The angiographic appearance of coronary collateral vessels was mainly observed in patients with coronary occlusion before operation and with graft occlusion (plus occlusion of the native artery) after operation. Both these subsets revealed the same pattern of segmental dysfunction: At rest, wall motion was preserved to some extent by collateral vessels; however, during stress, akinesia developed. This behavior was different from the pattern in coronary occlusion without revascularization (group A) in which left ventricular function was severely impaired at rest. Thus, a protective effect of collateral vessels on myocardial function is evident at rest but not after stress.

A significant protective effect of coronary collateral vessels on resting myocardial function was reported[3,4,23–25] in patients with complete coronary occlusion. In patients with coronary stenosis no protective

effect of collateral vessels on regional function could be shown.[1,2] Bourassa et al.[23] described impaired motion in eight patients but normal motion in five patients after the development of coronary collateral vessels in patients with occluded grafts and native arteries, thus supporting our observation that collateral vessels have some protective effect on ventricular function at rest. Among patients with 75 to 99 percent coronary stenosis we found no significant difference in regional function in those with and without collateral vessels, but among patients with complete occlusion we found significantly better regional function in those with than in those without collateral vessels.

The collateral supply generally is manifested angiographically when stenosis exceeds 90 percent luminal obstruction[3,24]; with less severe stenosis collateral vessels are rarely seen. Exact evaluation of the effect of collateral vessels in coronary stenosis would therefore require selection of patients with exactly the same degree of stenosis of over 90 percent. A simpler approach to defining the functional significance of collateral vessels is to evaluate their effect on complete vessel occlusion when the postobstructive myocardium is entirely dependent on collateral supply. In a recent study from this laboratory[26] it was shown by intraoperative measurement of poststenotic pressure and postocclusion graft flow hyperemia that collateralized occlusion of a vessel is comparable with 90 percent pure stenosis and that coronary reserve is partly restored by collateral vessels.

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Influence of Preoperative Left Ventricular Function on Results of Homograft Replacement of the Aortic Valve for Aortic Stenosis

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The effect of preoperative left ventricular function on early and late prognosis was assessed in 103 patients with aortic stenosis who underwent left ventricular cineangiography before homograft replacement of the aortic valve. The patients were separated into two groups: Group A (58 patients) with an ejection fraction of 0.46 or more and Group B (45 patients) with an ejection fraction of 0.45 or less. The two groups were compared with respect to clinical and hemodynamic data as well as operative result. There was poor correlation between clinical data and left ventricular function. In Group A there were three early deaths (5.2 percent) and three late deaths (5.2 percent) compared with no early and six late deaths (13.3 percent) in Group B during the follow-up period of 12 to 102 months (mean 43 months). Most patients in Group B showed considerable symptomatic improvement but less than that observed in Group A. Forty-two patients (13 in Group A and 29 in Group B) underwent repeat cardiac catheterization and coronary angiography. Improvement in left ventricular function as assessed by radial analysis of segmental wall motion and ejection fraction was observed in 20 of the 29 patients in Group B. Failure of left ventricular function to improve was associated with additional coronary artery disease in the majority of patients. It is concluded that poor left ventricular function does not increase the risk of aortic valve replacement for aortic stenosis and that improvement in left ventricular function can be expected in the majority of patients.

Left ventricular function is thought to be one of the main determinants of the early and long-term results of aortic valve replacement for aortic stenosis.[1–4] The exact role of left ventricular function, its response to correction of the valve lesion and the factors affecting it remain uncertain. To clarify this problem, we analyzed a group of patients who underwent homograft replacement of the aortic valve for aortic stenosis.

Methods

Selection of patients: Between August 1969 and November 1976 a total of 570 patients underwent homograft replacement of the aortic valve at Harefield Hospital. The dominant hemodynamic lesion was aortic stenosis in 249 patients, including 103 who had a left ventricular cineangiogram available for analysis. These 103 patients are the subject of this communication. Among the remaining 146 patients with dominant aortic stenosis, hemodynamic studies were performed at other institutions in 87 patients, the aortic valve could not be crossed in 34, and the left ventricular angiogram was technically unsatisfactory for analysis in 25. All 103 patients included in this study had clinically severe aortic stenosis with a calculated valve area of less than 0.7 cm^2. No patient had more than grade 1/4 aortic regurgitation as judged by aortic root angiography.

The patients were separated into two groups on the basis of measurement of preoperative ejection fraction, calculated from standard formulas during

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a period free of ectopy early in the angiogram to minimize the effects of contrast medium. Group A (58 patients) consisted of 33 male and 25 female patients aged 8 to 69 years (mean 52 years) with an ejection fraction equal to or greater than 0.46. Group B (45 patients) consisted of 40 men and only 5 women aged 30 to 71 years (mean 53 years) with an ejection fraction equal to or less than 0.45. An ejection fraction of 0.45 or more has been considered to give optimal results after coronary bypass grafting.[5] Clinical data, including preoperative severity and duration of symptoms, postoperative morbidity and mortality, symptomatic improvement and changes in the electrocardiogram were studied in both groups. Changes in left ventricular function and hemodynamic findings were evaluated in 42 patients, reinvestigated after aortic valve replacement.

Hemodynamic and angiographic study: Preoperatively all patients underwent right and left heart catheterization after overnight fasting and premedication with atropine, 0.01 mg/kg, and diazepam, 0.15 mg/kg. After measurement of peak systolic aortic valve gradient and left ventricular end-diastolic pressure, a single plane left ventricular cineangiogram was performed in the right anterior oblique projection with the injection of approximately 45 ml of 70 percent sodium iothalamate (Conray 420®) injected at a flow rate of 15 ml/sec using a Contrac injector and filmed at 50 frames/sec using an Arriflex camera. Preoperative coronary angiography was performed in 76 patients using the technique described by Sones or Judkins. Coronary angiography was performed only as a routine procedure in patients with aortic valve disease in this center from 1974 onward. Before 1974, coronary angiography was restricted to patients who presented with severe angina. A 50 percent or greater luminal stenosis in a major coronary artery was taken as evidence of significant coronary artery disease. Cardiac output was calculated from the Fick principle, the arterial line being in the ascending aorta. Aortic valve area was calculated using the formula of Gorlin and Gorlin,[6] derived from mean left ventricular and aortic pressures. Left ventricular and aortic pressure tracings obtained on withdrawal across the aortic valve were superimposed.

Surgery: The operative procedure in each case consisted of the insertion of a fresh, antibiotic sterilized unstented homograft using two suture lines with coronary perfusion at 30°C.[7] Fourteen patients (five in Group A, nine in Group B) underwent combined valve replacement and aortocoronary bypass grafting. Isolated valve replacement was performed in seven further patients with coronary artery disease who underwent operation before our experience with combined valve replacement and bypass grafting.

Forty-two patients gave informed consent for elective reinvestigation with right and left heart catheterization and coronary and left ventricular cineangiography. The repeat studies were performed at intervals ranging between 3 and 88 months (mean 24 months) after valve replacement as part of an ongoing study into the long-term function and durability of homograft valves.

Assessment of left ventricular function: This was accomplished using computerized, quantitative, radial analysis of segmental wall motion derived from the single plane left ventricular cineangiogram.[8] The cineangiogram was projected on a Vanguard projector and end-diastolic and end-systolic frames were digitized using an ultrasonic coordinate converter (Graf/Pen) on line with an HP 2100A computer. Ejection fraction was determined using the single plane area-length method.[9] End-diastolic and end-systolic frames were superimposed using the mid point of the aortic valve and the geometric center of gravity of the end-systolic frame as fixed reference points.[8] Radials were automatically plotted from the center of gravity to the ventricular perimeter at 4° increments in a clockwise direction starting at the mid point of the aortic valve. Segmental wall motion was expressed as the percent change in length of such radials from end-diastole to end-systole and was plotted against the radial angle around the ventricular perimeter. An abnormality was defined as five consecutive radials (20° or 5 percent of the ventricular perimeter) greater than 2 standard deviations outside control values obtained in a group of normal angiograms. No correction for X-ray magnification was made. Statistical analysis of data was performed using the Student *t* test and chi squared.

The severity of left ventricular hypertrophy as manifested in the electrocardiogram was assessed in three grades: Grade I, a normal electrocardiogram, with the tallest R wave or the deepest S wave in any lead being less than 20 mm; Grade II, the tallest R wave in any of the standard leads being greater than 20 mm or the tallest R wave and the deepest S wave in the precordial leads being greater than 25 mm; and Grade III, the findings in Grade II with the addition of associated ST-T abnormalities in the absence of digitalis. Left ventricular hypertrophy with ST-T changes in the presence of digitalis was downgraded by one grade.

Results

Preoperative Findings

Symptoms and functional state: All patients were symptomatic at the time of operation. In Group A, 35 patients (60 percent) presented with angina and dyspnea, dyspnea alone was present in 17 patients (30 percent) and angina alone in 6 patients (10 percent). In Group B, 27 patients (60 percent) presented with angina and dyspnea, dyspnea alone occurred in 11 patients (24 percent) and angina alone in 7 patients (16 percent). The prevalence of effort syncope was greater in patients in Group A, occurring in 15 patients (26 percent) compared with only 2 patients (5 percent) in Group B; otherwise the distribution of symptoms was similar in the two groups. At the time of operation 28 patients (48 percent) in Group A were in New York Heart Association[10] functional class III or IV compared with 35 patients (78 percent) in Group B. The duration of symptoms in patients in Group A ranged between 4 and 84 months (mean 24 months) and in Group B between 4 and 96 months (mean 32 months).

Cardiac size and hypertrophy: The heart size as measured from the cardiothoracic ratio in a standard chest X-ray film ranged between 0.42 and 0.68 (mean 0.51) in patients in Group A and between 0.48 and 0.72 (mean 0.53) in patients in Group B. The difference in heart size was not statistically significant although 35 patients (60 percent) in Group A had a cardiothoracic ratio greater than 0.50.

The severity of left ventricular hypertrophy as manifested in the electrocardiogram was assessed in 94 patients. In the remaining nine patients the presence of conduction defects precluded analysis of left ventricular hypertrophy. Of the 54 patients suitable for analysis in Group A, 39 patients (72 percent) showed the changes of left ventricular hypertrophy on voltage criteria with additional ST-T segment abnormalities in the absence of digitalis. Eleven patients (20 percent) showed left ventricular hypertrophy on voltage criteria alone,

and in four patients (8 percent) the electrocardiogram was judged to be normal. Of the 40 patients in Group B, 36 (89 percent) showed evidence of left ventricular hypertrophy with ST-T changes in the absence of digitalis. Left ventricular hypertrophy on voltage criteria alone was present in three patients (8 percent) and the electrocardiogram was normal in one patient (3 percent). The electrocardiogram showed evidence of previous transmural myocardial infarction in one patient (1.7 percent) in Group A and in 6 patients (13.3 percent) in Group B ($P < 0.05$). Preoperative conduction defects were present in 11 patients (19 percent) in Group A and in 18 patients (40 percent) in Group B ($P < 0.05$). The mean frontal QRS vector was widely distributed throughout both groups with no evidence of a greater left axis shift in patients with poor left ventricular function.

Hemodynamic data: The preoperative hemodynamic findings in the two groups are summarized in Table I. There was no statistically significant difference between the two groups in peak systolic aortic valve gradient, cardiac index or aortic valve area, although there was a tendency toward lower cardiac index and smaller aortic valve area in patients with poor left ventricular function. Left ventricular end-diastolic pressure was significantly greater ($P < 0.05$) in patients in Group B. The peak systolic aortic gradient was less than 50 mm Hg in six patients (one in Group A and five in Group B). However, all these patients had evidence of severe aortic stenosis as judged by calculated aortic valve area and all five patients in Group B had an ejection fraction less than 0.35.

Coronary arterial anatomy: Preoperative coronary angiography was performed in 36 of the 58 patients in Group A and in 40 of the 45 patients in Group B. The coronary arteries were judged normal in 30 patients (83 percent) in Group A; single vessel disease was present in 2 patients (6 percent), double vessel disease in 1 patient (3 percent) and triple vessel disease in 3 patients (8 percent). The coronary arteries were normal in 24 patients (60 percent) in Group B; single vessel disease was present in 6 patients (15 percent), double vessel disease in 7 (18 percent) and triple vessel disease in 3 (7 percent).

Postoperative Findings

Postoperative mortality: In Group A, there were three early deaths (5.2 percent) within 30 days of operation and three late deaths (5.2 percent) during a follow-up period ranging from 12 to 102 months (mean 43 months). All three late deaths occurred unexpectedly, one at 24 months after operation and two at 36 months after operation. Two deaths were presumed to be due to arrhythmias: In one case the preoperative electrocardiogram had shown variable bifascicular block and in the second left bundle branch block with a prolonged P-R interval. The third death was related to overwhelming viral infection. Postmortem examination showed that the aortic homograft was functioning well in all three patients, and there was no evidence of coronary artery disease.

During the same follow-up period there were no early deaths in Group B, but six late deaths (13.3 percent) that occurred at 28, 48, 48, 52, 55 and 72 months, respectively, after operation. All six patients died with congestive heart failure, and five of the patients were found to have severe coronary artery disease. At postmortem examination the aortic homograft was found to be functioning well in five of the patients but was stenotic and calcified in one patient. Survival in the two groups is represented in an actuarial manner in Figure 1. At a follow-up period of 6 years there was no significant difference in mortality between the two groups. After 6 years there appeared to be a greater mortality in patients with poor left ventricular function (Group B), although the number of patients followed up for this length of time is too small to give accurate data.

Postoperative clinical improvement: All patients in Group A had symptomatic improvement after operation (Fig. 2), and 51 patients (98 percent) were reclassified in functional class 1. In Group B all but two patients had symptomatic improvement, and 35 (90 percent) were in functional class 1. Regression of left ventricular hypertrophy by electrocardiogram was more consistent in Group A than in Group B. Complete regression of left ventricular hypertrophy occurred in 42 patients (88 percent) in Group A but in only 19 patients (54 percent) in Group B (Fig. 3).

Postoperative segmental wall motion on angiography: Forty-two patients (13 in Group A and 29 in Group B) were reinvestigated with cardiac catheterization and coronary angiography 3 to 88 months (mean 24 months) after aortic valve replacement. Sixteen patients were reinvestigated within 12 months of operation, and of these only three were investigated within 6 months of operation. Computerized radial analysis of segmental wall motion was performed on the preoperative and postoperative angiograms of all patients reinvestigated.

Analysis of the preoperative angiogram of the 13 patients in Group A showed a normal contraction pattern in 8 patients (62 percent) and localized segmental wall abnormalities in 5 patients (38 percent). After operation the contraction pattern remained unchanged in the eight patients with previously normal wall motion. In the five patients with localized wall

TABLE I

Preoperative Hemodynamic Findings in 103 Patients With Aortic Stenosis

	Group A	Group B
Peak systolic aortic valve gradient (mm Hg)	35–165 (92)	35–135 (84)
Left ventricular end-diastolic pressure (mm Hg)	3.0–34.0 (10.6)	4.0–32.0 (17.0)
Ejection fraction	0.46–0.80 (0.65)	0.14–0.45 (0.33)
Cardiac index (liters/min per m^2)	1.7–5.2 (2.7)	1.0–3.0 (2.1)
Aortic valve area (cm^2)	0.3–0.7 (0.52)	0.2–0.62 (0.39)

Figures in parentheses indicate mean values.

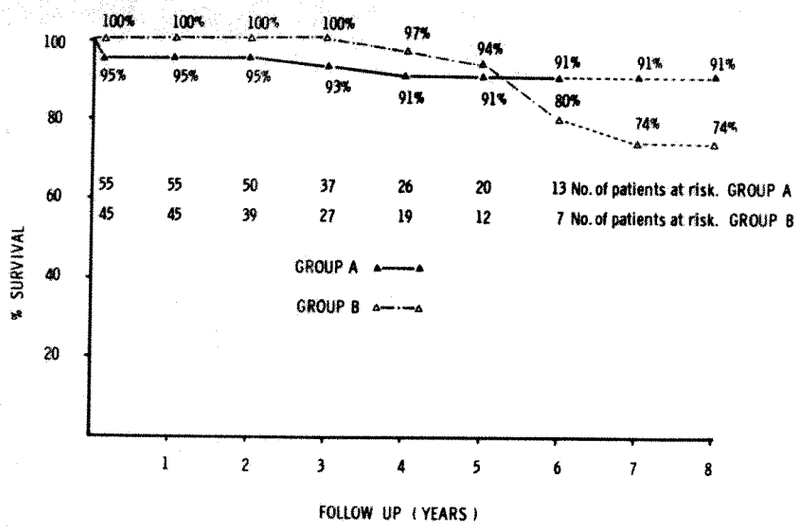


FIGURE 1. Actuarial analysis of survival after homograft replacement of the aortic valve in relation to preoperative left ventricular function.

motion abnormalities, contraction returned to normal in three and was unchanged in two.

Analysis of the preoperative angiogram of the 29 patients in Group B showed a normal contraction pattern in 3 patients (10 percent) despite depressed ejection fraction. Localized abnormalities of wall motion were present in 6 patients (20 percent), and generalized or global hypokinesia was present in 20 patients (70 percent). After operation, the three patients with originally normal wall motion had no change in contraction pattern. The contraction pattern returned to normal in five of the six patients with localized wall abnormalities and remained unchanged in one. Among 20 patients with generalized hypokinesia, the contraction pattern improved in 12 (returning to normal in 8) and remained unchanged in 8. Thus, after operation, the pattern of left ventricular contraction was entirely within normal limits in 16 (55 percent) of the 29 patients in Group B and was improved in a further 4 patients.

Changes in ejection fraction: Changes in left ventricular contraction pattern correlated well with changes in ejection fraction (Fig. 4). After operation, 20 of the 29 patients in Group B had an ejection fraction exceeding 0.55. In Group B as a whole the ejection fraction increased significantly after operation from a mean of 0.35 to a mean of 0.59 ($P < 0.001$). Nine patients failed to show significant improvement in ejection fraction, and all nine had significant abnormalities of segmental wall motion. All nine patients were in functional class IV at the time of operation and had a left ventricular end-diastolic pressure exceeding 20 mm Hg. Five of the nine patients had significant coronary artery disease. Two of the five had undergone combined valve replacement and coronary bypass grafting, but both had sustained a myocardial infarction before operation. The remaining three had not had coronary bypass grafting; two of these sustained a perioperative myocardial infarction and both have since died. As expected, the ejection fraction in patients in Group A did not increase

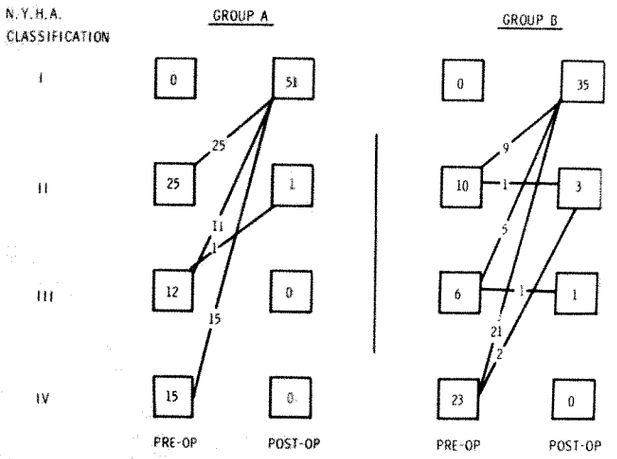


FIGURE 2. Regression of symptoms after aortic valve replacement. N.Y.H.A. = New York Heart Association functional classification; POST-OP = postoperative; PRE-OP = preoperative.

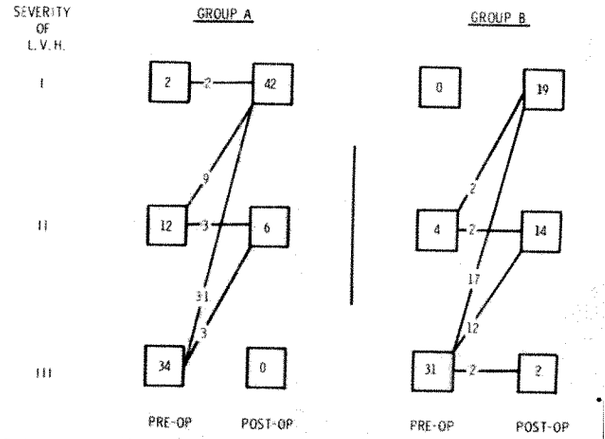


FIGURE 3. Regression of left ventricular hypertrophy (L.V.H.) after aortic valve replacement. Abbreviations as in Figure 2.

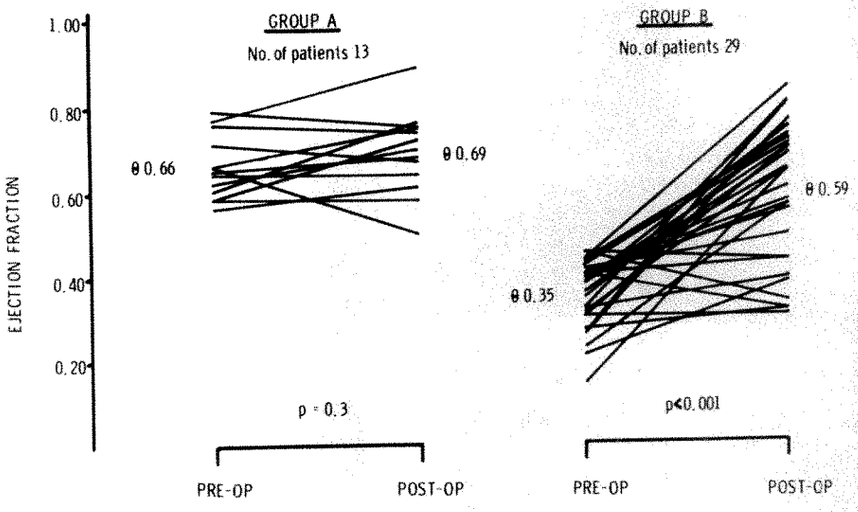


FIGURE 4. Changes in ejection fraction in 42 patients restudied after aortic valve replacement. θ = mean; p = probability; other abbreviations as in Figure 2.

significantly from its preoperative valve of 0.46 or more. One patient, who underwent combined valve replacement and coronary bypass grafting, showed significant deterioration in ejection fraction after occlusion of a bypass graft.

Left ventricular end-diastolic pressure and cardiac index: In patients in Group B there was a substantial decrease in the left ventricular end-diastolic pressure from a mean of 17.4 to a mean of 7.2 mm Hg (P <0.001) (Fig. 5). Left ventricular end-diastolic pressure did not change significantly in patients in Group A (P <0.2). Similarly, in patients in Group B cardiac index increased significantly from a mean of 2.1 to a mean of 3.0 liters/min per m^2 (P <0.05) (Fig. 6). There was no significant increase in cardiac index in patients in Group A.

Correlation of changes in ventricular function with coronary artery disease: Of the 42 patients restudied 23 were found to have normal coronary arteries. Analysis of preoperative left ventricular segmental wall motion in this group showed that the contraction pattern was normal in 7 patients (30 percent), showed localized abnormalities of wall motion in 4 patients (17 percent) and generalized hypokinesia in 12 patients (53 percent). At subsequent reinvestigation wall motion was unchanged in the seven patients with originally normal wall motion. Of the four patients with localized wall abnormalities wall motion returned to normal in three and was unchanged in one. Of the 12 patients with generalized hypokinesia, wall motion improved in 8 (returned to normal in 6) and was unchanged in 4. Thus, 11 (69 percent) of the 16 patients with abnormal wall motion before operation showed significant improvement after operation.

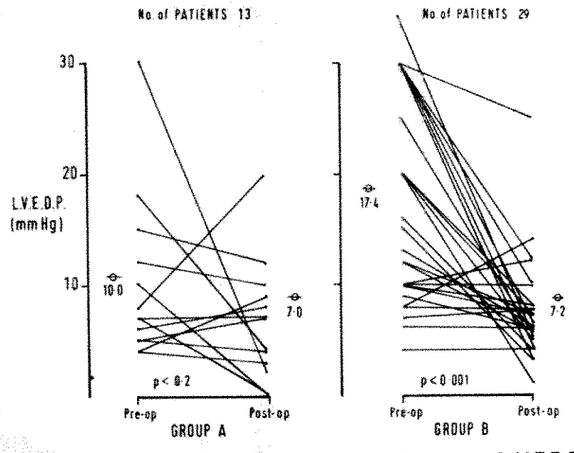


FIGURE 5. Changes in left ventricular end-diastolic pressure (L.V.E.D.P.) in 42 patients restudied after aortic valve replacement. Abbreviations as in Figures 2 and 4.

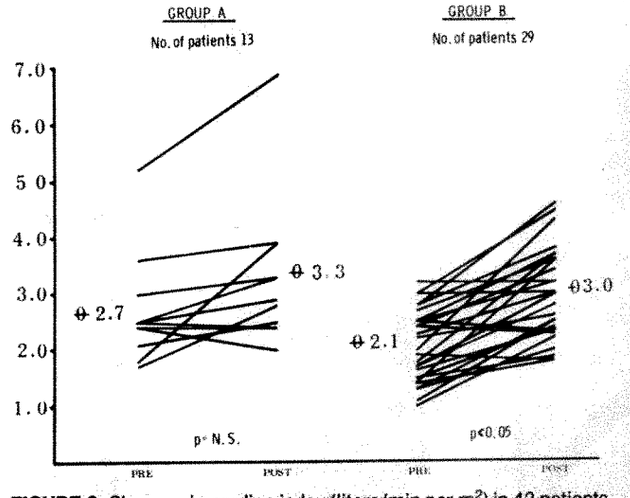


FIGURE 6. Changes in cardiac index (liters/min per m^2) in 42 patients restudied after aortic valve replacement. θ = mean; N.S. = not significant; POST = postoperative; PRE = preoperative.

Nineteen of the restudied 42 patients were found to have coronary artery disease. Analysis of preoperative segmental wall motion showed that 4 of the 42 patients (21 percent) had a normal pattern of left ventricular contraction, 8 (42 percent) had localized abnormalities of wall motion and 7 (37 percent) had generalized hypokinesia. Twelve of these 19 patients subsequently underwent combined valve replacement and coronary bypass grafting. In 4 of the 12 wall motion was initially normal and was unchanged after operation; among 5 patients with initial localized abnormalities wall motion returned to normal in 4 and was unchanged in 1 (after occlusion of the bypass graft) and among 3 patients with generalized hypokinesia, wall motion was unchanged in 2 who had had a preoperative myocardial infarction and was improved in 1 patient although there was a residual localized wall motion abnormality. Thus, of the 12 patients undergoing combined valve replacement and coronary bypass grafting, 8 (75 percent) showed a normal pattern of contraction after operation.

Seven patients with coronary artery disease underwent isolated valve replacement. Five patients in this group had generalized hypokinesia preoperatively; postoperatively, the contraction pattern improved in three patients and was unchanged in two. Two further patients had localized abnormalities of wall motion preoperatively; the contraction pattern was unchanged in one and improved in one. However, despite the improved contraction pattern in four of the seven patients who had coronary artery disease but did not undergo bypass grafting, three of the four subsequently died after a myocardial infarction and the subsequent development of ventricular failure. Of the three patients showing no improvement in segmental wall motion, two had a perioperative myocardial infarction and both subsequently died. Changes in segmental wall motion were closely reflected in changes in ejection fraction (Fig. 7).

Postoperative aortic valve function: Aortic regurgitation was present after operation in 9 of the 42 patients re-investigated but was never more severe than grade 1/4 as assessed with aortic root angiography. Although patients did not routinely undergo exercise testing at the time of cardiac catheterization, no patient showed a gradient across the homograft valve at rest.

Illustrative cases: Figure 8 shows examples of radial analysis of segmental wall motion before and after operation. *In Figure 8A* the preoperative analysis shows marked generalized hypokinesia. Two years after operation the contraction pattern returned to normal, and this change was associated with an increase in ejection fraction from 0.29 to 0.66.

Figure 8B illustrates marked preoperative segmental hypokinesia affecting principally the inferior surface and, to a lesser extent, the anterior surface. Three years after operation, which did not include coronary bypass grafting, the contraction pattern returned to normal despite the presence of diffuse triple vessel disease, and the ejection fraction increased from 0.31 to 0.81. However, 6 years after operation this patient sustained a major myocardial infarction with the subsequent development of left ventricular failure, and he died 2 months later.

Figure 8C illustrates severe left ventricular hypokinesia affecting the inferior surface in a patient with normal coronary arteries; the contraction pattern improved after valve replacement.

Figure 8D shows severe preoperative generalized hypokinesia that was not changed in subsequent investigation 18 months after operation. This patient had normal coronary arteries and, despite satisfactory valve function, died with left ventricular failure 2 years after valve replacement.

Discussion

Determinants of left ventricular function in aortic stenosis: Changes in ejection fraction have been widely used in the assessment of left ventricular function following cardiac surgery and as a prognostic guide in the surgical treatment of coronary and valvular heart

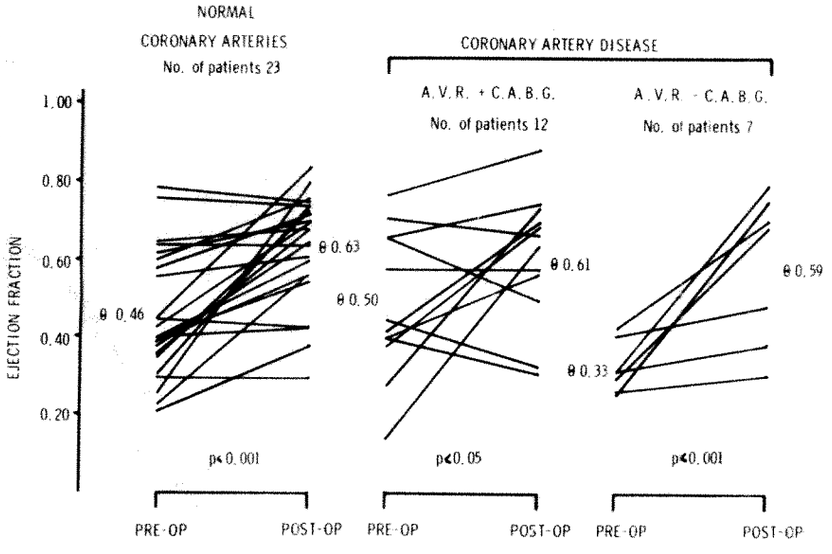


FIGURE 7. Changes in ejection fraction in relation to coronary artery disease in 42 patients restudied after aortic valve replacement (A.V.R.). C.A.B.G. = coronary bypass grafting; other abbreviations as in Figures 2 and 4.

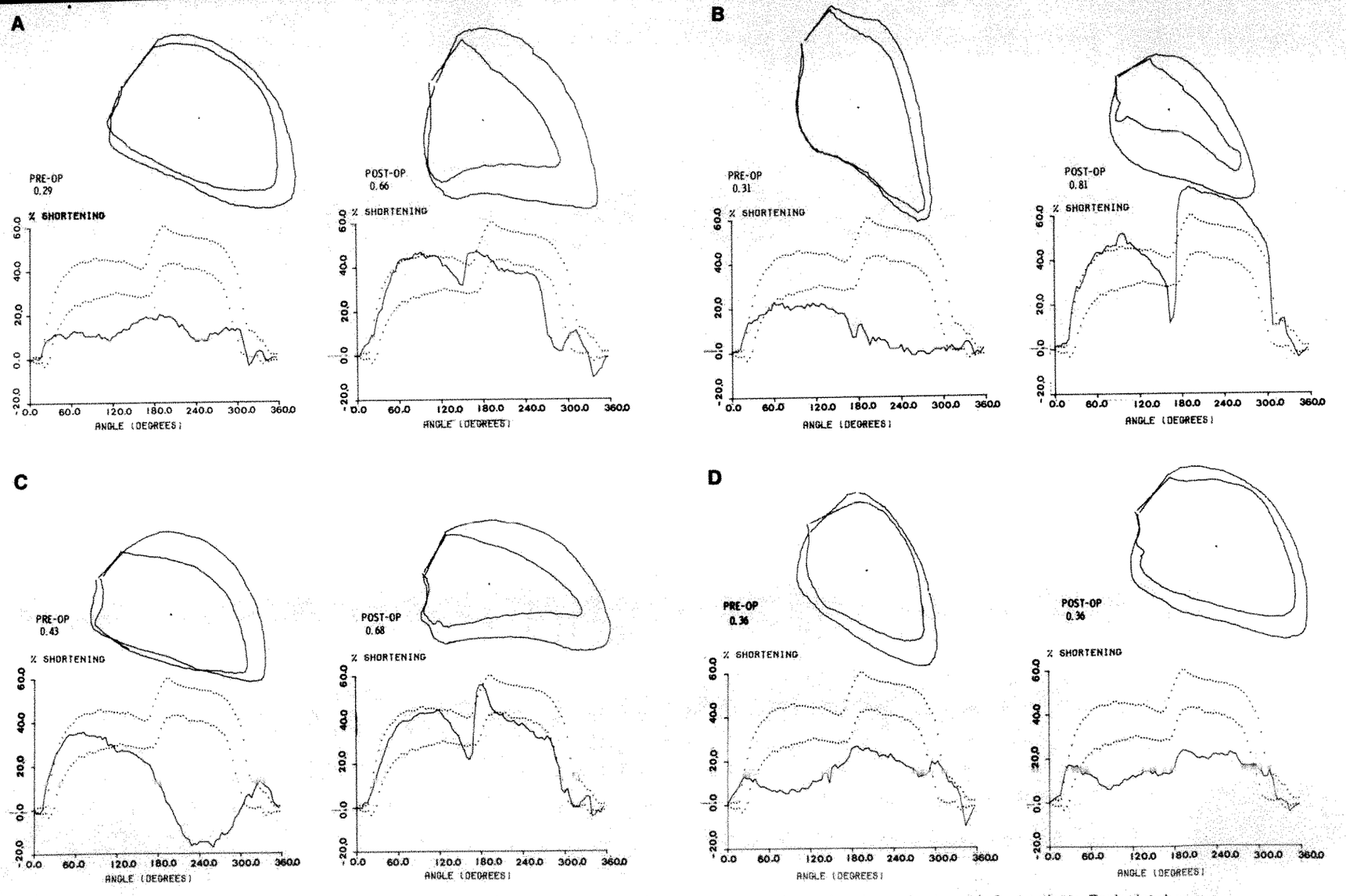


FIGURE 8. Radial analysis of segmental wall motion before (PRE-OP, **left panels**) and after (POST-OP, **right panels**) aortic valve replacement in four patients. Each plot shows the percent shortening (**vertical axis**) against the radial angle (**horizontal axis**). The **dotted lines** represent ±1 standard deviation from the mean values obtained in a group of normal patients (see text for details). The numbers under PRE-OP and POST-OP are ejection fractions.

disease.[4,11,12] In patients undergoing valve replacement, changes in afterload may, in theory, alter ejection fraction in the absence of any change in myocardial performance. This was suggested by the work of Lewis and Gotsman,[13] who found a linear and inverse relation between ejection fraction and peak systolic gradient across the aortic valve in six patients with aortic stenosis. We have not confirmed these findings in 103 patients in whom there was no correlation between systolic gradient and ejection fraction. More recent work[14] has suggested that left ventricular afterload is not a major determinant of poor myocardial performance and, therefore, subsequent changes in left ventricular function are not simply a reflection of decrease in afterload. Furthermore, no change in ejection fraction was observed in our series after operation in patients with good preoperative left ventricular function despite reduction in left ventricular afterload. This finding was in marked contrast to the increase in ejection fraction seen in patients with poor left ventricular function. Compared with ejection fraction, quantitative analysis of left ventricular segmental wall motion provides a more sensitive index of overall left ventricular contraction because it allows analysis of changes in ventricular segments that may not be revealed by measurements such as ejection fraction that indicate overall myocardial performance. Improvement in one myocardial segment may be accompanied by deterioration in another without change in ejection fraction.

Etiology of poor left ventricular function in patients with aortic stenosis: remains uncertain. Lewis and Gotsman[13] showed that increasing severity of aortic stenosis as judged by systolic gradient was associated with reduction in ejection fraction and diastolic compliance. Similarly Krayenbuehl et al.[15] found evidence of impaired contractility with increasing left ventricular muscle mass in patients with aortic stenosis or aortic regurgitation and concluded that the extent of hypertrophy was more important for the decreased contractility than the nature of the stimulus to hypertrophy. In the present series we could find no evidence on the basis of clinical or hemodynamic variables including aortic valve area, cardiac index and peak systolic valve gradient that poor left ventricular function was associated with more severe degrees of aortic stenosis. The duration of aortic stenosis may play an important role in the etiology of left ventricular dysfunction, although we were unable to establish this in our study. Because most patients do not present until symptoms are established it is not possible to determine with any degree of accuracy the duration of hemodynamically significant valve obstruction. This could only be established by serial investigation of patients with various degrees of aortic stenosis.

Role of coronary artery disease: Poor left ventricular function was not related to age in this series. However, there was a marked preponderance of men in this group with impaired left ventricular function, but this greater prevalence was not associated with an increased incidence of coronary artery disease. Linhart et al.[16] drew attention to the large incidence of coronary artery disease in patients with aortic stenosis and the high operative mortality in these patients. Since then, the reported incidence of coronary artery disease in patients with aortic stenosis has ranged between 22 and 64 percent.[17–21] Although in our series only 40 of the 45 patients in Group B (low ejection fraction) underwent coronary angiography before operation, 40 percent had coronary artery disease. Despite normal coronary arteries myocardial perfusion may be severely reduced in patients with aortic stenosis.[22] A prolonged systolic ejection time and tachycardia may reduce diastolic coronary filling and coronary perfusion particularly to subendocardial zones.[23] Additional factors restricting coronary flow include abnormal flow patterns in the aortic root,[24] a low mean aortic pressure and increased left ventricular systolic wall tension.[25] Coronary artery disease further compounds the restriction of myocardial blood flow. This is probably reflected in our series by the finding of a greater prevalence of localized abnormalities of segmental wall motion in patients with coronary artery disease, although such abnormalities were not exclusive to patients with coronary artery disease.[26]

Clinical predictors of poor left ventricular function: It has been difficult to predict poor left ventricular function on the basis of clinical criteria. Although the incidence and severity of shortness of breath were greater in those with poor left ventricular function this symptom was not exclusive to these patients. Our Groups A and B did not differ significantly in the duration of symptoms, heart size or electrocardiographic signs of left ventricular hypertrophy. However, conduction defects were more common in patients with poor left ventricular function. In approximately one quarter of the patients in Group B poor left ventricular function was already established despite only minimal symptoms.

Postoperative improvement in left ventricular function: Although most patients with poor preoperative left ventricular function derived considerable benefit from operation, gaining both relief of symptoms and improvement in the quality of life, the overall improvement was less consistent than in those with normal preoperative left ventricular function. There were no early deaths in the patients with a low preoperative ejection fraction, and actuarial analysis showed no difference in survival between the two groups of patients at a follow-up time of 6 years. Smith et al.[27] in a series of 19 patients with aortic stenosis and impaired left ventricular function, reported an early mortality rate of 21 percent with a 3 year survival rate of 74 percent. The discrepancy between these data and those of our series may be related to differences in the prevalence of coronary artery disease or to improved techniques of myocardial preservation. It has been our practice to combine moderate degrees of hypothermia with continuous coronary perfusion in patients undergoing both isolated aortic valve replacement and in patients undergoing additional coronary bypass grafting.

Combined coronary bypass grafting and aortic valve replacement: As in previously reported series,[28,29] improvement in left ventricular function oc-

curred in a high proportion of patients reinvestigated and, in our series, occurred at least in the short-term in patients with coronary artery disease who did not undergo bypass grafting. However, subsequent follow-up has shown that despite initial improvement in left ventricular function in patients with coronary disease without bypass grafting, the condition of most has deteriorated as a consequence of progression of coronary artery disease and myocardial infarction with associated deterioration in left ventricular function. This group constituted a major cause of mortality. Many reports[30–33] have shown that coronary bypass grafting can be safely combined with aortic valve replacement. In a previous report[34] of 40 patients with aortic stenosis undergoing combined valve replacement and coronary bypass grafting at this center, both the early and late mortality rates were not significantly different from those of patients undergoing either isolated valve replacement or isolated coronary bypass grafting. Similarly the incidence of perioperative and late infarction in this group was not significantly different from that of patients undergoing coronary bypass grafting alone. The poor prognosis of triple vessel coronary artery disease, particularly when associated with impaired left ventricular function, is well established.[35–37] The good clinical results, with low early and late mortality in combined aortic valve replacement and coronary artery bypass grafting, have encouraged us to believe that this is a valuable procedure that in the longer term may favorably influence the prognosis and reduce late myocardial infarction in patients with aortic stenosis and ischemic heart disease.

Advantages of homograft aortic valve: Changes in left ventricular function after valve replacement are also probably influenced in part by the type and efficiency of the valve substitute used. A homograft valve provides almost ideal hemodynamic characteristics providing that significant regurgitation is absent. A previous report from this center[38] showed that trivial or mild aortic regurgitation was present in 23 percent of patients at 5 years after homograft replacement of the aortic valve and significant regurgitation in only 1.2 percent. Although systolic murmurs were common, no systolic gradient across the homograft could be demonstrated at rest or on exercise in 72 patients undergoing routine cardiac catheterization after operation. These results have encouraged us to continue to perform homograft valve replacement and, when necessary, additional coronary bypass grafting in patients with poor left ventricular function.

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Use of Apexcardiography To Evaluate Left Ventricular Diastolic Compliance in Human Beings

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The relation between various relative amplitude measurements of the left apexcardiogram and internally derived indexes of diastolic compliance of the left ventricle was studied in 29 patients. Simultaneous high fidelity recordings of the left apex tracing and left ventricular pressure were obtained in 11 patients without left ventricular disease (group I) and 18 patients with congestive cardiomyopathy (group II). In 204 normal subjects the ratio of the *A* wave amplitude to the total diastolic deflection (A/D ratio) of the left apexcardiogram was 31.4 ± 11.4 (mean ± standard deviation) percent, the ratio of the *A* wave amplitude to the total height (A/H ratio) 8.9 ± 4.3 percent and the D/H ratio 30.4 ± 14.7 percent. The A/D and A/H ratios were significantly ($P < 0.001$ and $P < 0.005$) increased in group II (69.2 ± 12.2 percent and 16.8 ± 8.2 percent, respectively); they were within normal limits in group I. In contrast, the D/H ratio was within normal limits in both groups of patients.

The A/D ratio correlated significantly better with specific compliance ($\Delta V/\Delta P \cdot V$) ($r = -0.87$) than did the A/H ratio ($r = -0.53$), whereas similar correlations were obtained with end-diastolic volume compliance (dV/dPV) ($r = -0.61$ and $r = -0.64$, respectively). In contrast, the D/H ratio correlated significantly only with end-diastolic distensibility index (dV/dP) ($r = -0.52$). It is concluded that *A* wave amplitude/total diastolic deflection (A/D) ratio and, to a lesser degree, the *A* wave amplitude/total height (A/H) ratio of the left apexcardiogram correspond best to diastolic compliance and are useful noninvasive measurements of this property of the left ventricle.

The evaluation of the diastolic properties of the left ventricle has mainly depended on data obtained with invasive methods. Many investigators[1–9] have developed methods of determining the diastolic pressure-volume relations of the left ventricle in man and estimating diastolic compliance. These measurements have been utilized to aid in interpreting some signs and symptoms related to decreased left ventricular diastolic distensibility[1,2] or to gain prognostic information.[4]

The left apexcardiogram has been shown to reflect left ventricular events accurately in a qualitative[10–15] and also in a quantitative fashion.[16–19] The *A* wave of the left apex tracing mirrors diastolic events directly recorded from the left ventricle,[10,20] reflecting the impact of the late atrial contribution on the filling or already filled left ventricular cavity. In patients with various cardiovascular diseases, an abnormal increase in the height of the *A* wave has been described.[21–24] Several authors[25–29] have found that the ratio of the height of the *A* wave and of the total diastolic deflection to the total vertical amplitude as well as the ratio of the *A* wave amplitude to the diastolic deflection of the apex tracing correlated with left ventricular end-diastolic pressure.

The purpose of this study was to assess the validity of these relative amplitude measurements derived from the left apexcardiogram as

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noninvasive indexes of diastolic compliance of the left ventricle. Specifically, we compared the correlations between these noninvasive measurements and various internally derived indexes of left ventricular compliance as well as the sensitivity of the former for distinguishing patients without or with only slight left ventricular disease and normal diastolic compliance from patients with congestive cardiomyopathy.

Methods

Subjects: Apexcardiograms were recorded in 233 subjects. All showed sinus rhythm; the QRS complex did not exceed 0.10 second in duration. In 204 healthy volunteers apex tracings alone were recorded, whereas in 29 patients the apexcardiograms were obtained during cardiac catheterization. In the patients who underwent catheterization premedication consisted of 10 mg of chlordiazepoxide given orally 1 hour before the procedure.

The 204 normal subjects ranged in age from 17 to 60 years (mean ± standard deviation 38 ± 18 years). None had a previous history of heart disease and, before registration, all had had normal findings on a complete physical examination, 12 lead electrocardiogram and chest X-ray film.

Patients with hemodynamic and angiographic data were separated into two subgroups for the purpose of analysis. Patients without or with only slight pressure or volume overload of the left ventricle constituted group I; patients with congestive cardiomyopathy constituted group II.

Group I (control subjects) comprised 11 patients, 7 women and 4 men. Three had a functional murmur. Three had a small patent ductus arteriosus and one a small ventricular septal defect, all of them with a left to right shunt of less than 15 percent of the pulmonary flow. One patient had a small atrial septal defect (left to right shunt of 35 percent of pulmonary flow), one a slight pulmonary valve stenosis (pressure gradient 18 mm Hg), one a mild form of coarctation of the aorta (pressure gradient 9 mm Hg) and one a stenosis of the truncus brachiocephalicus and slight arterial hypertension.

Group II comprised 18 patients, 16 men and 2 women. None of the 18 patients had evidence of amyloidosis or hemochromatosis or a previous history of respiratory infection or perimyocarditis; in 3 patients alcohol abuse may have been a factor in the cardiomyopathy. The functional class (New York Heart Association criteria[30]) was class I in five patients (28 percent), class II in six (33 percent), class III in four (22 percent) and class IV in three patients (17 percent) with clinical and radiologic evidence of severe congestive heart failure. The hemodynamic and angiographic data revealed that seven patients had no valve disease, but two of these seven had labile arterial hypertension. Nine patients showed mild mitral regurgitation; one had additionally slight aortic stenosis (pressure gradient 15 mm Hg by planimetry) as well as slight aortic incompetence, and one had mild arterial hypertension. One patient had a small patent ductus arteriosus associated with labile arterial hypertension and one a small ventricular septal defect with a left to right shunt of 12 percent of the pulmonary flow.

No patient who underwent catheterization had signs of localized wall motion abnormalities on left ventricular cineangiography or evidence of coronary artery disease on selective coronary arteriography.

Apexcardiography: All apexcardiographic and pressure tracings were recorded on an Electronics for Medicine DR-8 or DR-16 photographic recorder at a paper speed of 200 mm/sec (Fig. 1 and 2). All apex tracings were obtained at the

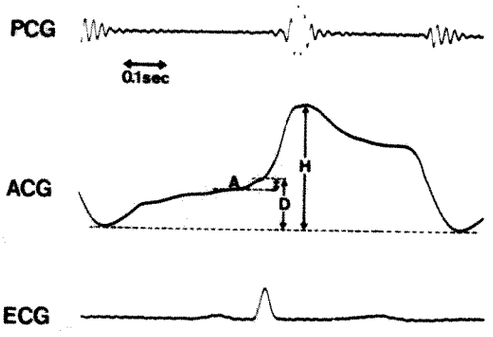


FIGURE 1. The method of measurement for apexcardiographic relative amplitude ratios. A simultaneous left apexcardiogram (ACG), electrocardiogram (ECG) and phonocardiogram (PCG) were taken from a normal subject. A = height of the A wave; D = total diastolic deflection; H = total vertical height of the apex tracing. Paper speed is 200 mm/sec. In this example, the A/D ratio is 22.7 percent, the A/H ratio 9.4 percent and the D/H ratio 40 percent.

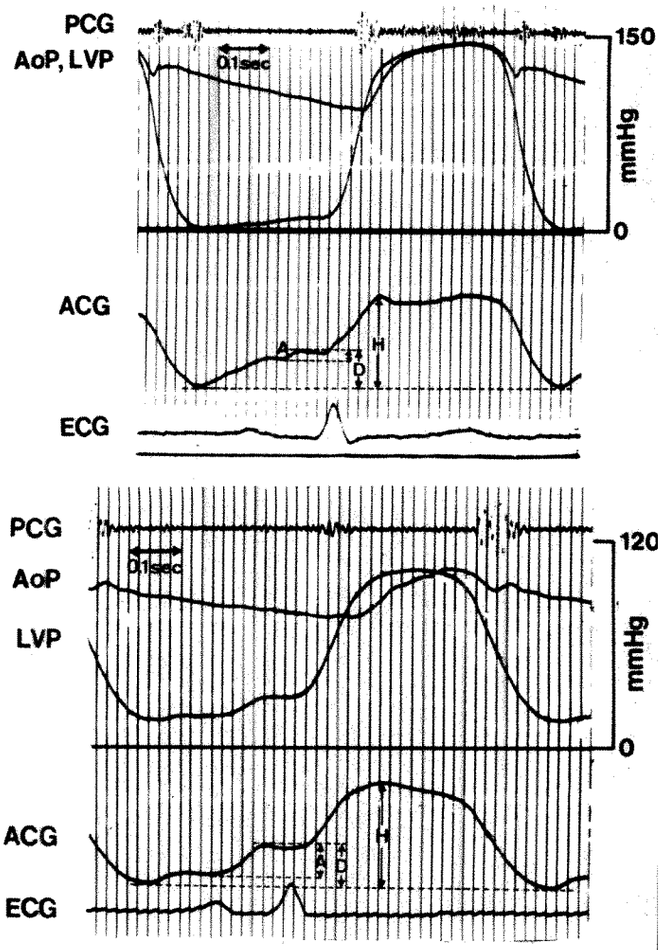


FIGURE 2. Simultaneous recordings of the left apexcardiogram (ACG), left ventricular pressure (LVP) and aortic pressure (AoP) in a normal patient (group I) **(top)** and a patient with congestive cardiomyopathy **(bottom)**. Abbreviations as in Figure 1.

site of the maximal apical impulse with the patient in the left recumbent position. The recording device has been previously described[15,17–19]; the pulse transducer constructed in our laboratory consists basically of a Marey capsule with the interior surface directly connected to a Bio-Tec transducer (BT-250T). This system has an infinite time constant.[15] Figure 1 shows how the amplitude of the waves of the apexcardiogram was measured.

The following fractions of amplitude of apexcardiographic waves were calculated and expressed as a percent: the relative magnitudes of the *A* wave in relation to the total outward movement (A/H ratio) and to the total diastolic deflection (A/D ratio) as well as the relative magnitude of the diastolic deflection in relation to the total vertical deflection (D/H ratio). These methods of expressing the apexcardiographic data were originated by Benchimol and Dimond,[11] Rios and Massumi[25] as well as Voigt and Friesinger,[26] who first introduced the A/H, D/H and A/D indexes, respectively. For each measurement five heart cycles were averaged.

Left heart catheterization and angiography: After right heart catheterization a Statham SF_1-tip manometer was introduced into the left ventricle either by a retrograde route or after puncture of the septum. The pressure in the ascending aorta was measured using a second SF_1-tip manometer or a Statham P23Db pressure transducer connected to a red Oedmann catheter.

The following hemodynamic measurements were made: left ventricular systolic and end-diastolic pressures as well as the lowest left ventricular pressure recorded in early diastole, systolic and diastolic aortic pressures and the difference between the left ventricular end-diastolic and the lowest early diastolic pressure. The left ventricular end-diastolic pressure was taken at the junction of the downslope of the *A* wave with the upstroke of the left ventricular pressure curve.[8]

Left ventricular cineangiograms were performed in the right anterior oblique position about 1 hour after the pressures and apex tracings were recorded. Contrast dye (Urographin 76 percent, Schering, Berlin) was delivered in amounts of 25 to 45 ml by an electrocardiogram-triggered power injector (Contrac, Siemens, Zurich). Angiographic determinations of left ventricular end-diastolic and end-systolic volumes were made using the single plane method of Greene et al.[31] The ejection fraction was calculated according to the area-length method of Dodge et al.[32] All cineangiographic measurements were corrected for magnification, and all volumes were expressed in milliliters per square meter of body surface area.

Calculations of diastolic compliance: "Compliance" is a general term relating to the overall passive diastolic pressure-volume characteristics of the ventricle. Because no single index of ventricular compliance has been accepted as the standard, compliance was assessed in the present study using the following five formulas:

1. Reciprocal of the passive elastic modulus = $\Delta V/\Delta P$.
2. Specific compliance (SC) = $\Delta V/\Delta P \cdot 1/Ves$.
3. Slope of the ln P-V relation (k) = $(\ln P - \ln b)/Ved$.
4. End-diastolic volume distensibility index = $dV/dP = 1/k \cdot P$.
5. End-diastolic volume compliance = $dV/dPV = 1/k \cdot P \cdot Ved$.

In these formulas, ΔV = left ventricular diastolic volume change or angiographic stroke volume calculated as the end-diastolic volume index minus the end-systolic volume index in ml/m^2; ΔP = left ventricular diastolic pressure change calculated as the end-diastolic pressure minus the lowest early diastolic pressure; P = left ventricular end-diastolic pressure; Ved = end-diastolic volume index; Ves = end-systolic volume index; k represents the slope of the logarithmic pressure-volume relation assuming a constant positive pressure intercept (b) at 0 volume of 0.43, which has been found in the in vitro dog heart[3]; and dV/dP represents the inverse slope of a tangent to the pressure-volume curve at end-diastole. The theory and derivations of formula 1 were described in detail by Diamond and Forrester,[1] those of formula 2 by Smith et al.,[4] and those of formulas 3 to 5 by Gaasch et al.[3,7–9]

Results

Hemodynamic indexes: The average values and ranges of the hemodynamic and apexcardiographic measurements are given in Table I. In the control group (group I), the average value for left ventricular end-diastolic pressure was 10 mm Hg; the average values for end-diastolic volume index, end-systolic volume index, stroke volume index and ejection fraction were 85 ml/m^2, 26 ml/m^2, 59 ml/m^2 and 69 percent, respectively. These values are in agreement with previously reported data in a group of normal subjects from our laboratory.[33] The average values for specific compliance, the reciprocal of the passive elastic modulus, the slope of the logarithmic pressure-volume relation, the end-diastolic distensibility index and end-diastolic compliance were 0.372 mm Hg^{-1}, 9.03 ml/m^2 per mm Hg, 0.038, 2.76 ml/m^2 per mm Hg and 3.29 mm $Hg^{-1} \times 10^{-2}$, respectively. These values are in accord with those previously reported from this laboratory[34] and by others.[1,3,8] The average end-diastolic pressure as well as end-diastolic volume and end-systolic volume indexes of the left ventricle in the patients with congestive cardiomyopathy (group II) were significantly higher (21 mm Hg, 159 ml/m^2 and 97 ml/m^2, respectively) and the average ejection fraction significantly lower (41 percent), whereas the stroke volume index was not statistically different from that of the control group.

The average values for specific compliance, slope of the ln P-V relation and end-diastolic compliance in group II were statistically reduced (0.095 mm Hg^{-1}, 0.026 and 1.61 mm $Hg^{-1} \times 10^{-2}$, respectively). In contrast, the average values for the reciprocal of the passive elastic modulus and end-diastolic distensibility index in group II were not statistically different from control values in group I. Furthermore, the average lowest left ventricular pressure in early diastole was statistically higher in group II. In contrast, the average difference between left ventricular systolic, early diastolic and end-diastolic pressure as well as diastolic aortic pressure were not statistically different in the two groups.

Apexcardiographic measurements: The relative amplitude of the *A* wave to total diastolic deflection and to total height of the apex tracing as well as the relative magnitude of the total diastolic deflection to total height showed no significant correlation with age in the normal subjects. In these subjects the mean values of these measurements did not differ between women and men.

Magnitude of *A* wave in relation to total diastolic deflection (A/D ratio): This ratio averaged in normal subjects 31.4 ± 11.4 percent (mean ± standard deviation) with a range of 9.1 to 54.3 percent. The mean value of this ratio was significantly increased in group II (69.2

TABLE I

Apexcardiographic and Cardiac Catheterization Data (mean ± 1 standard deviation and range)

	Group I (no. = 11)	Group II (no. = 18)	*P** Value
Age (yr)	31 ± 14; (19–59)	42 ± 10; (28–62)	<0.02
Heart rate (beats/min)	77 ± 18; (43–112)	76 ± 19; (59–117)	<0.02
A/D ratio (%)	27.6 ± 12.8; (25.0–41.7)	69.2 ± 12.2; (44.4–90.9)	<0.001
A/H ratio (%)	8.3 ± 4.1; (3.5–16.7)	16.8 ± 8.2; (3.8 –31.3)	<0.005
D/H ratio (%)	25.5 ± 10.3; (14.0–45.8)	24.5 ± 11.5; (5.1–42.2)	NS
LVP (mm Hg)	129/4/10 ± 21/2/2; (101–159/1–6/6–12)	126/11/21 ± 30/9/10; (90–182/2–32/11–41)	NS/<0.001/<0.005
ΔP (mm Hg)	6.8 ± 1.9; (4–10)	10.1 ± 5.6; (4–27)	NS
AoP (mm Hg)	129/83 ± 21/12; (101–159/62–96)	125/81 ± 29/14; (90–179/55–108)	NS/NS
EDVI/ESVI (ml/m^2)	85/26 ± 13/7; (62–97/16–34)	159/97 ± 49/42; (83–230/38–166)	<0.001/<0.001
SVI (ml/m^2)	59 ± 13; (38–81)	62 ± 20; (39–102)	NS
EF (%)	69 ± 8; (61–84)	41 ± 13; (23–59)	<0.001
ΔV/ΔP (ml/m 2 per mm Hg)	9.03 ± 2.20; (7.13–14.75)	8.09 ± 5.79; (2.41–23.25)	NS
Specific compliance (mm Hg^{-1})	0.372 ± 0.094; (0.210–0.506)	0.095 ± 0.062; (0.029–0.213)	<0.001
k (−)	0.038 ± 0.006; (0.029–0.210)	0.026 ± 0.009; 0.015–0.044)	<0.005
dV/dP (ml/m^2 per mm Hg)	2.76 ± 0.81; (1.75–4.39)	2.57 ± 1.57; (0.71–5.56)	NS
dV/dPV (mm Hg^{-1} × 10^{-2})	3.29 ± 1.14; (2.49–6.36)	1.61 ± 0.81; (0.53–3.12)	<0.005

* *P* (probability) values obtained with unpaired Student's *t* test.

A/D ratio = relative amplitude of the *A* wave to the total diastolic deflection of the apex tracing; A/H ratio = relative amplitude of the A wave to the total vertical height of the apex tracing; AoP = ascending aortic pressure (systolic/diastolic); D/H ratio = relative amplitude of the total diastolic to the total vertical deflection of the apex tracing; ΔP = difference between left ventricular end-diastolic pressure and the lowest left ventricular pressure in early diastole; ΔV/ΔP = reciprocal of the passive elastic modulus; dV/dP = left ventricular end-diastolic distensibility index; dV/dPV = left ventricular end-diastolic compliance; EDVI = left ventricular end-diastolic volume index; EF = ejection fraction; ESVI = left ventricular end-systolic volume index; k = slope of the logarithmic pressure-volume relation; LVP = left ventricular pressure (systolic/lowest diastolic/end-diastolic); NS = not significant ($P > 0.05$); SVI = stroke volume index.

± 12.8 percent), but it was within normal limits (27.6 ± 12.2 percent) in group I. Correlation coefficients were calculated for the total cohort of the patients undergoing catheterization using internally derived measures as independent variables and the A/D ratio as a dependent variable (Table II). The highest degree of correlation was found with specific compliance ($r = -0.87$, $P < 0.001$) (Fig. 3, top). The A/D ratio showed, further, highly significant ($P < 0.001$) correlations with end-systolic volume index ($r = +0.68$) and with end-diastolic compliance ($r = -0.61$) (Fig. 3, bottom). Statistically less significant ($P < 0.01$) were the positive relation with end-diastolic volume index ($r = +0.56$) and the negative relations with the slope of the ln P-V relation ($r = -0.47$) and with the reciprocal of the passive elastic modulus ($r = -0.39$). Weak positive associations were also present with left ventricular end-diastolic pressure as well as with the difference between end-diastolic and lowest early diastolic pressures.

Magnitude of *A* wave in relation to total vertical deflection (A/H ratio): This widely used apexcardiographic index averaged in normal subjects 8.9 ± 4.3 percent (range 2.1 to 17.2 percent). This average value is in agreement with values found by Rios and Massumi[25] and Parker et al.[27] in groups of normal subjects. The A/H ratio was statistically higher (16.8 ± 8.2 percent, $P < 0.005$) in group II and within normal limits (8.3 ± 4.1 percent) in group I. Linear regression analysis was performed between the A/H ratio and internally derived measures (Table II). There was a highly significant ($P < 0.001$) correlation between the A/H ratio and end-diastolic compliance ($r = -0.64$) and a less significant ($P < 0.01$) correlation between the A/H ratio and end-diastolic distensibility index ($r = -0.55$) as well as specific compliance ($r = -0.53$). Furthermore, significant positive relations were present with the left ventricular end-diastolic pressure ($r = +0.65$, $P < 0.001$) and with the lowest early diastolic pressure ($r = +0.44$,

TABLE II

Correlations (*r* values) Between Apexcardiographic and Internally Derived Indexes in 29 Patients Undergoing Cardiac Catheterization

	LVEDP	LVP_0	ΔP	EDVI	ESVI	SVI	ΔV/ΔP	SC	k	dV/dP	dV/dPV
A/D	+0.46*	(+0.25)	+0.49†	+0.56†	+0.68‡	(−0.15)	−0.39*	−0.87‡	−0.47†	(−0.08)	−0.61‡
A/H	+0.65‡	+0.44*	+0.56†	(+0.19)	(+0.25)	(−0.11)	(−0.25)	−0.53†	(−0.04)	−0.55†	−0.64‡
D/H	+0.38	(+0.31)	(+0.24)	(−0.18)	(−0.20)	(−0.02)	(−0.17)	(−0.06)	(+0.26)	−0.52†	(−0.27)

*,†,‡ = *P* (probability) values of <0.05, <0.01 and <0.001, respectively.
Values in parentheses indicate that the correlation was not significant ($P > 0.05$).

$P < 0.05$) as well as with the difference between these pressures ($r = +0.56$, $P < 0.01$).

Magnitude of diastolic deflection in relation to total vertical deflection (D/H ratio): The mean value of the D/H index in our normal subjects—30.4 ± 14.7 percent (range 13.1 to 44.5 percent)—was somewhat higher than the average value found by Rios and Massumi[25] in 50 normal subjects. The average value for this ratio was slightly, but not significantly, lower than normal in both group I (25.5 ± 10.3 percent) and group II (24.5 ± 11.5 percent). Thus, the mean value of the D/H ratio was within normal limits in both groups of patients. Table II shows the relations between the D/H ratio and internally derived indexes. A significant ($P < 0.01$) negative correlation was present with the end-diastolic distensibility index ($r = -0.52$). There was poor, although significant, positive correlation with left ventricular end-diastolic pressure ($r = +0.38$).

Discussion

Changes in ventricular volume and myocardial firmness were suggested as two of the major mechanisms in the genesis of the apical displacement and its graphic representation, the apexcardiogram.[35,36] Recent reports[14–16,37] have noted that the configuration, time course and slope of the left apexcardiogram are significantly correlated with left ventricular pressure. It has also been shown[17–19] that time intervals, which can easily be measured in the apex tracing and its first derivative, correlate with indexes of myocardial function derived internally during systole. Several authors[25–29] have demonstrated that the relative height of various diastolic waves of the left apex tracing are related to left ventricular end-diastolic pressure. However, the importance of this relation is rather limited because a meaningful interpretation of left ventricular end-diastolic pressure in the analysis of left ventricular function can be made only when the relation between filling pressure and end-diastolic volume is known. For this purpose, we compared in this study three relative amplitude indexes derived from the left apexcardiogram with several internally derived indexes of left ventricular diastolic compliance using simultaneous high fidelity apex and left ventricular pressure tracings recorded just before angiocardiography.

Relative *A* wave amplitude of left apexcardiogram: The *A* wave of the apex tracing has been related to left ventricular function. The precise mechanism of the *A* wave elevation in the diseased or poorly functioning left ventricle is not known. However, one might expect such a ventricle to respond poorly to the added burden of atrial systole because impaired distensibility leads to disproportionate intraventricular pressure-volume changes that are reflected by an increase in the precordial *A* wave. Some have considered the *A* wave of the apex tracing an indicator, not necessarily quantitative, of changes in the level of left ventricular end-diastolic pressure and have attempted to demonstrate this by comparing this pressure with the amplitude of the *A* wave in relation to the total diastolic or total vertical deflection of the apexcardiogram.

Ratio of *A* wave height to total diastolic deflection (A/D ratio): The relation between this index and left ventricular end-diastolic pressure was first examined by Voigt and Friesinger[26] who did not find any useful correlation. The most important finding of our study is the close inverse correlation of the A/D ratio with specific compliance ($r = -0.87$). Further, all patients with values over 44 percent for the A/D ratio had congestive cardiomyopathy. Thus, the A/D ratio separated these patients from those without left ventricular disease.

We have considered the reasons for the close relation between the A/D ratio and specific compliance. Because calculation of specific compliance requires several measurements of pressure and volume, regression analyses between the A/D ratio and left ventricular end-diastolic pressure, lowest early diastolic pressure,

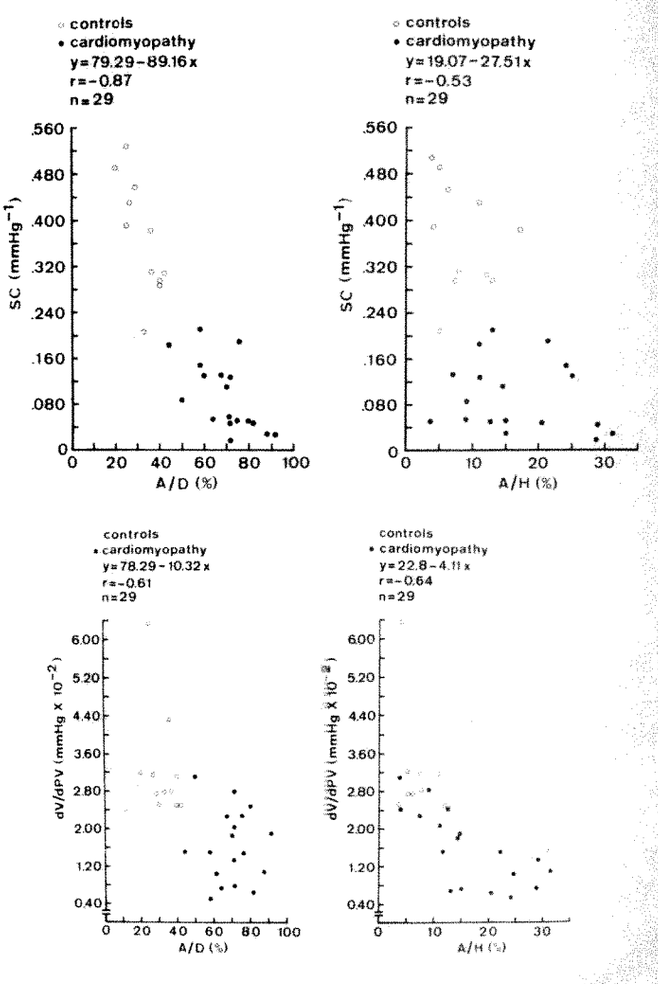


FIGURE 3. Linear regression analyses. **Top,** between specific compliance (SC) and the A/D **(left)** and the A/H **(right)** ratios. **Bottom,** between left ventricular end-diastolic volume compliance (dV/dPV) and the A/D **(left)** and the A/H **(right)** ratios.

stroke volume index as well as end-systolic volume index were performed to investigate which of these variables correlated best with the A/D ratio. The A/D ratio showed the highest degree of correlation with end-systolic volume index. Smith et al.[4] reported that, in patients with coronary artery disease, "the end-systolic volume predicts the size of abnormally contracting segments"; we thus have a reasonable explanation for the ability of the A/D ratio in our study to distinguish between patients with a "bad" from those with a "good" left ventricle. In this context, it must be emphasized that the correlation between the A/D ratio and specific compliance was higher than the correlation between the A/D ratio and any single volume or pressure value. The A/D ratio also correlated highly significantly with left ventricular end-diastolic compliance (Fig. 3, bottom) and less significantly with the slope of the logarithmic pressure-volume relation as well as the reciprocal of the passive elastic modulus. These observations indicate that the A/D ratio calculated noninvasively from the apex tracing is a useful index of the diastolic properties of the left ventricle because it correlates significantly with several internally derived and widely used indexes of diastolic compliance.

Ratio of *A* wave height to total vertical deflection (A/H ratio): An increase in the A/H ratio was found in disease states in which "the reserve of distensibility" of the left ventricle is impaired, usually in the presence of left ventricular hypertrophy.[10] In aortic valve disease, idiopathic hypertrophic subaortic stenosis and hypertension, an abnormal increase in the A/H ratio was reported.[21–24] Ginn et al.[29] demonstrated that patients with coronary artery disease responded to exercise by a near doubling of the A/H ratio and, further, that an elevated A/H ratio during an episode of ischemia was appreciably reduced with nitroglycerin therapy. Similar data were obtained by Benchimol and Dimond.[10,11] Gibson et al.[28] found a close correlation between the A/H ratio and the slope of the late diastolic left ventricular pressure/diameter relation, as calculated with use of a combined ultrasonic technique. They first suggested that the A/H ratio is related to left ventricular late diastolic stiffness.

In our study, the A/H ratio had a highly significant correlation with left ventricular end-diastolic compliance ($r = -0.64$) and significantly lower correlations with end-diastolic distensibility index as well as specific compliance. However, the highest correlation was observed between the A/H ratio and left ventricular end-diastolic pressure ($r = +0.65$). Thus, because the end-diastolic distensibility index and end-diastolic compliance are highly dependent on left ventricular end-diastolic pressure—requiring both the natural logarithm of left ventricular end-diastolic pressure and this pressure itself for their calculation—the mentioned relations between the A/H ratio and the invasively derived indexes of compliance are logical in retrospect. On the other hand, the A/H index did not correlate with the slope of the logarithmic pressure-volume relation or with the reciprocal of the passive elastic modulus. Moreover, 11 of 18 patients (62 percent) with cardiomyopathy showed a normal value for the A/H ratio (that is, less than 17.5 percent), although 5 of them (45 percent) had an elevated left ventricular end-diastolic pressure. This is in agreement with the findings of other authors.[27,28] Our data thus demonstrate that the A/H ratio is related to internal indexes of diastolic compliance mainly because of its correlation with left ventricular end-diastolic pressure; it is rather poorly related to specific compliance and not related to the slope of the logarithmic pressure versus volume relation.

A/D ratio versus A/H ratio: Comparison of the relations of the A/D and A/H ratios with internal indexes of diastolic compliance shows that the A/D ratios (1) correlated with four of the five internal indexes of compliance, and (2) showed the highest degree of correlation obtained in this study, namely, with specific compliance. In this context, the relation between the A/D ratio and the slope of the logarithmic pressure-volume relation should be emphasized. The latter represents an index of elasticity in the intact ventricle and describes the overall relation between left ventricular end-diastolic pressure and volume, suggesting whether a pressure-volume curve is shifted to the right or to the left (the lower value for this internal index of compliance in our patients with congestive cardiomyopathy indicating a shift to the right). With respect to ability to distinguish between control subjects and patients with congestive cardiomyopathy, the A/D ratio separated the two groups of patients, whereas the A/H ratio did not.

Ratio of total diastolic deflection to total vertical deflection (D/H ratio): This index was first examined by Rios and Massumi,[25] who found a close relation between the D/H ratio and left ventricular end-diastolic pressure. In our comparison of the relations of the D/H ratio to internal indexes of diastolic compliance, we found only one significant association: the relatively weak inverse correlation with the end-diastolic distensibility index ($r = -0.52$). There was, further, a very poor correlation with the left ventricular end-diastolic pressure. Moreover, the D/H index did not differ from normal in the patients with cardiomyopathy. Thus, we found that the D/H index showed no useful correlation with invasively derived indexes of diastolic compliance, and did not separate patients with a normal from those with a diseased left ventricle.

Clinical implications: No single undisputed index for assessing diastolic compliance of the left ventricle in human beings is now available. Several quantitative methods of measuring compliance have been suggested. However, their use in the bedside evaluation of the diastolic properties of the left ventricle is limited because they require cardiac catheterization and angiography. Our study has demonstrated that two relative amplitude indexes, the *A* wave amplitude to total diastolic deflection (A/D) ratio and *A* wave amplitude to total height (A/H) ratio derived from the left apexcardiogram, a noninvasive technique, show good correlations with internally derived compliance indexes. However, the magnitude of the correlation coefficients does not permit one to estimate with sufficient confidence in an individual subject the corresponding invasive index of compliance on the basis of the noninvasive index. This

study establishes, furthermore, the superiority of the A/D index over the other apexcardiographic indexes.

We conclude that interpatient differences in left ventricular diastolic compliance can be evaluated quantitatively and noninvasively with the use of apexcardiography. However, the validity of these noninvasive ratios for assessing changes in diastolic compliance of the left ventricle in the same subject or in the presence of aortic or mitral valve disease as well as in coronary artery disease requires further investigation.

Acknowledgment

We express appreciation to Dr. Otto Hess and Kali Doxiadis for their contributions to this study.

Addendum

Since the preparation of this report, a pertinent article concerning the usefulness of a new apexcardiographic index for identifying subjects with ischemic heart disease has been published.[38]

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Lack of Correlation Between Echocardiographic Pulmonary Valve Morphology and Simultaneous Pulmonary Arterial Pressure

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Pulmonary valve echograms recorded simultaneously with right heart pressures were correlated with mean and end-diastolic pulmonary arterial pressures and the peak magnitude of the right atrial *a* wave in an attempt to predict noninvasively levels and changes in pulmonary arterial pressure. Satisfactory pulmonary valve echograms were obtained in 16 of 29 patients studied. No significant correlation was found between hemodynamic measurements and the echographic pulmonary valve *a* wave amplitude, diastolic E-F slope or the systolic opening B-C slope. Changes in hemodynamic measurements observed in serial observations were not associated with predictable changes in configuration of the pulmonary valve echogram. The combination of mid systolic pulmonary valve notching and an absent *a* wave was observed in more advanced degrees of pulmonary hypertension and was specific, but not sensitive, for that condition.

It has been suggested that the amplitude of the echographic pulmonary valve *a* wave is of value in the diagnosis of pulmonary hypertension.[1,2] Similar claims had been made for the pulmonary valve diastolic E-F slope,[2] systolic opening B-C slope,[1] and for the presence of mid systolic notching. The findings of these early reports raised the possibility that analysis of the pulmonary valve configuration from the echogram might provide noninvasive guides to assess the severity of pulmonary hypertension. To evaluate this potential, the features of the pulmonary valve echogram were correlated with simultaneously recorded pulmonary arterial and right atrial pressures.

Methods

Patients: In 29 patients undergoing hemodynamic monitoring for the evaluation and treatment of congestive heart failure, echography of the pulmonary valve was attempted and was successful in 16. These 16 patients, including 5 studied serially, form the study group. Twelve were men and four women. Eight patients had chronic ischemic heart disease, three had acute myocardial infarction, three had congestive cardiomyopathy, one had idiopathic hypertrophic subaortic stenosis and one had no detectable cardiac abnormality (Table I).

Echocardiography: Echocardiograms were obtained using the routinely employed method.[1] A commercially available echographic instrument with a variety of transducers was used, and recordings were made at 10, 25 and 100 mm/sec in all patients. Because of the presence of indwelling catheters, the studies were usually performed with the patient supine or lying on his left side.

Figure 1 shows the method used to measure the pulmonary valve *a* wave. The pulmonary valve diastolic E-F and systolic opening B-C slopes were measured according to previously described techniques.[1,2] When possible, the recordings were made during quiet respiration. The maximal *a* wave amplitude[2] was used when detectable respiratory variations were present (4 of 16 patients); otherwise,

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TABLE I

Clinical, Hemodynamic and Echocardiographic Data in 16 Patients

Case no.	Age (yr) & Sex	Diagnosis	Pressures (mm Hg) Pulmonary Artery RA_a	S/D (m)	ED $-RA_a$	Pulmonary Valve Echogram *a*	E-F	B-C	MS Notch	HR	CO
1	48 F	CHF	9	41/23 (30)	14	0.9	13–14	410	. . .	62	4.3
		CAD	4	36/18 (24)	24	0.6	9	340	. . .	60	
2	72 F	CHF CAD	20	52/35 (41)	15	0.0	−6	290	. . .	96	
3	67 M	MI	9	46/23 (31)	24	0.5	21	240	. . .	87	5.3
4	79 F	CC	10	44/22 (25)	12	1.7	15	440	. . .	92	3.8
5	53 M	CAD, MI	12	53/22 (30)	10	3.4	57	200	. . .	90	4.2
6	62 M	CC	6	50/22 (31)	16	1.5	−8	128	. . .	120	2.3
			16	55/35 (42)	19	0.8	0	650	Yes	110	4.3
7	55 M	HTN	10	79/32 (44)	22	1.9	10	440	. . .	60	4.7
		MI	6	66/32 (44)	26	1.3	7	310	. . .	90	2.7
			4	63/28 (39)	24	1.2	12	280	. . .	88	2.9
8	60 M	MI	8	36/13 (21)	5	2.6	12	640	. . .	80	3.4
9	66 M	CAD CHF	5	24/14 (18)	9	2.0	−4	440	. . .	96	3.0
10	52 M	CAD	4	52/25 (35)	21	1.6	4	500	. . .	72	3.9
11	44 F	CAD	5	51/18 (29)	13	0.3	7	224	. . .	84	3.0
12	60 M	CC	18	68/35 (46)	17	1.5	12	280	. . .	96	2.6
			10	37/19 (27)	9	1.7	−12	190	. . .	96	2.8
13	24 M	N	7	33/15 (21)	8	3.7	9	190	. . .	72	
14	77 M	CAD	1	21/10 (13)	9	1.7	8	426	. . .	90	5.6
			3	36/14 (20)	11	1.3	7	480	. . .	72	5.0
15	54 M	IHSS CHD	6	52/15 (21)	9	3.0	10	600	. . .	54	4.4
16	78 M	MI	8	79/30 (42)	22	0.0	18	340	Yes	102	4.0

a = pulmonary valve presystolic *a* wave (mm); B-C = early systolic slope of the pulmonary valve echo (mm/sec); CAD = coronary artery disease; CC = congestive cardiomyopathy; CHF = congestive heart failure; CO = cardiac output (liters/min); D = diastolic; ED = pulmonary arterial end-diastolic pressure; E-F = diastolic slope of pulmonary valve echo (mm/sec); HR = heart rate (beats/min); HTN = hypertension; IHSS = idiopathic hypertrophic subaortic stenosis; m = mean; MI = myocardial infarction; MS = mid systolic; RA_a = peak right atrial *a* wave; S = systolic.

the average of 10 beats was taken. Mid systolic notching was also sought.

Pressure measurements: Simultaneous recordings of phasic and mean pulmonary arterial pressures and right atrial pressure (Fig. 2) were obtained with use of a triple lumen Swan-Ganz 7F balloon-tipped catheter. Pressure measurements were obtained with a pressure transducer (Statham P23DB) interfaced with a Brush recorder. The pressure signal was also simultaneously recorded with the echogram by a fiberoptic recorder (Honeywell model 1856) by means of a multiplex circuit. Before each study the catheter was flushed and the transducer was balanced to zero pressure at the mid point of the anteroposterior thoracic diameter.

In four patients the study was repeated once, and in one patient it was repeated twice. The intervals between repeat studies ranged from 8 to 48 hours. In two patients the pulmonary valve echograms were recorded before and immediately after the withdrawal of the catheter across the pulmonary valve. The maneuver had no detectable influence on valve morphology.

Analysis of data: Data were analyzed by linear regression analysis of paired data. The mean pulmonary arterial, end-diastolic, pulmonary capillary wedge and peak right atrial *a* wave pressures were plotted against the echographic amplitude of the pulmonary valve *a* wave and the diastolic E-F and systolic opening B-C slopes. The differences between the

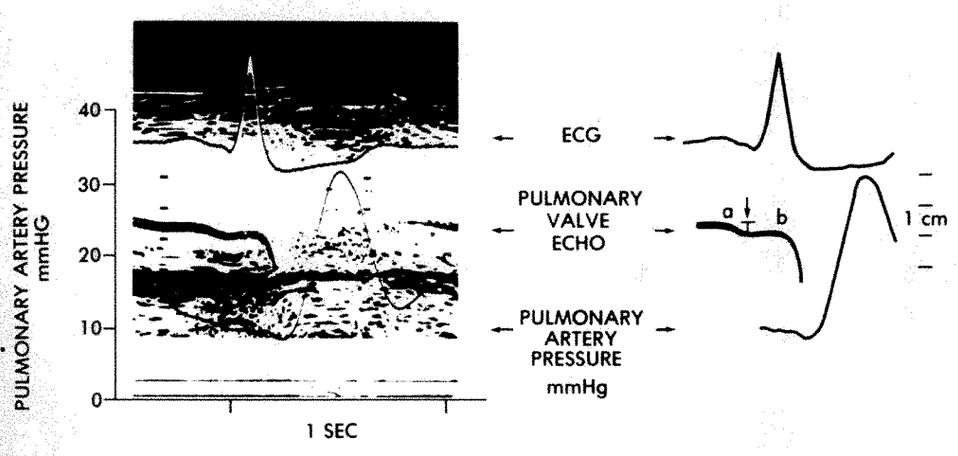


FIGURE 1. Simultaneous echocardiogram of the pulmonary valve and pulmonary arterial pressure tracing. Diagram demonstrates method of measuring amplitude of the *a* wave: a = onset and b = termination of the pulmonary valve *a* wave.

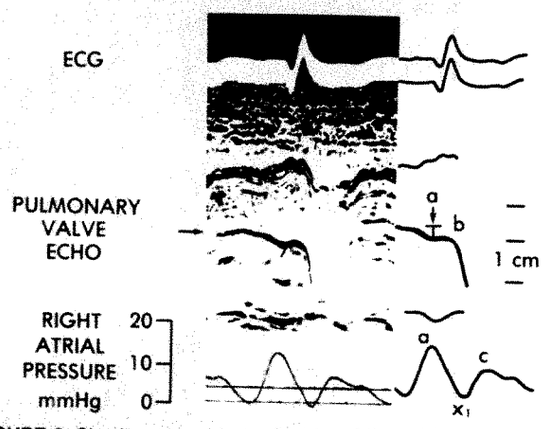


FIGURE 2. Simultaneous echocardiogram of the pulmonary valve and phasic right atrial pressure tracing. The diagram demonstrates the method of measuring *a* wave amplitude: a = onset and b = termination of the pulmonary valve *a* wave. ECG = electrocardiogram.

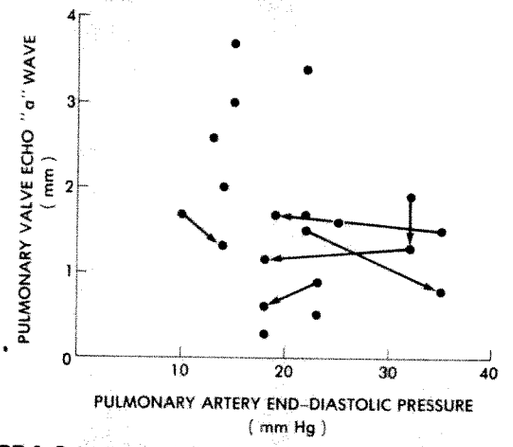


FIGURE 3. Pulmonary arterial end-diastolic pressure plotted against pulmonary valve *a* wave amplitude. **Arrows** connect points that represent serial measurements.

pulmonary arterial end-diastolic and peak right atrial *a* wave pressures were obtained and were also related to the amplitude of the pulmonary valve *a* wave.

Results

Echographic pulmonary valve *a* wave amplitude: The echocardiographic and hemodynamic measurements are shown in Table I. There was no statistically significant correlation between the pulmonary valve *a* wave amplitude and any of the hemodynamic variables measured (Fig. 3 and 4). A weak correlation was present between the differences of the pulmonary arterial end-diastolic and right atrial peak *a* wave pressure and the amplitude of the pulmonary valve *a* wave ($r = 0.49$ and $P < 0.05$) (Fig. 5). In this latter group, differences of less than 20 mm Hg showed the largest pulmonary valve *a* wave amplitude.

No correlations were found between the pulmonary valve diastolic E-F slope, systolic opening B-C slope and hemodynamic measurements (Fig. 6 to 8).

Serial measurements: The largest change in the five patients studied serially was a 29 mm Hg reduction in mean pulmonary arterial pressure (from 46 to 27 mm Hg). This was accompanied by a slight increase in the amplitude of the pulmonary valve *a* wave of 0.2 mm (from 1.5 to 1.7). In two other patients decreases in pulmonary arterial pressure (from 30 to 24 and from 44 to 39 mm Hg, respectively) were accompanied by slight decreases in pulmonary arterial *a* wave amplitude (from 0.9 to 0.6 and from 1.9 to 1.2 mm, respectively) (Fig. 4).

In our serial studies a mean decrease in mean pulmonary arterial pressure of 8 mm Hg was accompanied by a mean increase in pulmonary valve *a* wave amplitude of 0.03 mm. Figures 3, 4 and 6 to 8 show that the direction of magnitude of the pulmonary end-diastolic pressure changes bore no constant relation with the direction and magnitude of the pulmonary valve changes. The differences between the pulmonary arterial end-diastolic pressure and right atrial peak *a* wave

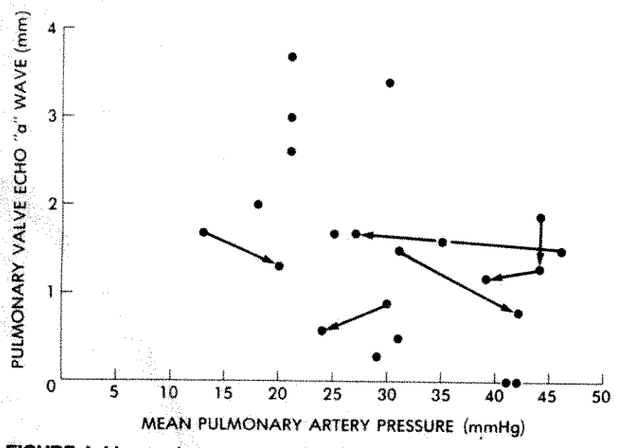


FIGURE 4. Mean pulmonary arterial pressure plotted against pulmonary valve echographic *a* wave amplitude. **Arrows** connect points that represent serial measurements.

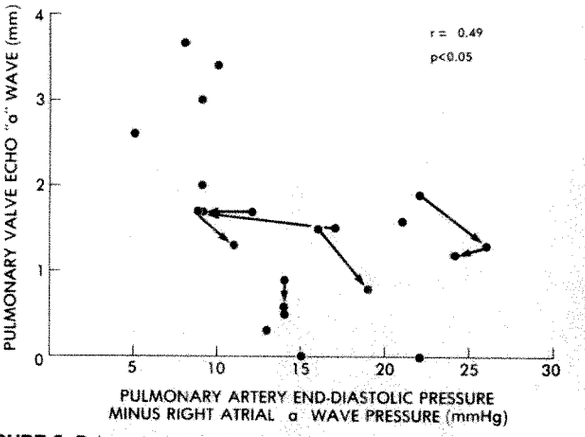


FIGURE 5. Pulmonary arterial end-diastolic pressure minus right atrial *a* wave pressure plotted against pulmonary valve echographic *a* wave amplitude. **Arrows** connect points that represent serial measurements.

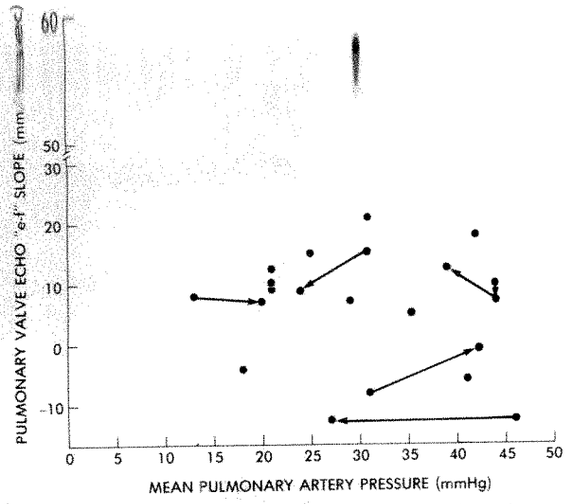


FIGURE 6. Mean pulmonary pressure plotted against the pulmonary echographic E-F slope. **Arrows** connect points that represent serial measurements.

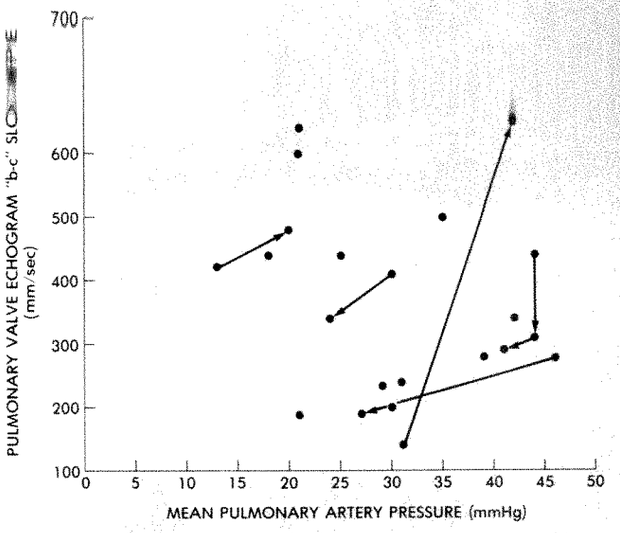


FIGURE 7. Mean pulmonary arterial pressure plotted against the pulmonary valve echographic B-C slope of initial valve opening. **Arrows** connect points that represent serial measurements.

pressures also failed to show predictable directional changes (Fig. 5).

Pulmonary valve mid systolic notching: Complete systolic recording of the pulmonary valve posterior leaflet echogram could be obtained in only eight patients. Mid systolic notching was present in two patients with a mean pulmonary arterial pressure of more than 40 mm Hg. In four other studies in which this pressure was also 40 mm Hg or more, either no notching was observed or incomplete tracings of the systolic pulmonary valve echograms prevented its recognition.

Discussion

Previous studies[1–3] have indicated that analysis of the echocardiographic morphology of the pulmonary valve, especially the pulmonary valve *a* wave amplitude, is useful in separating patients with normal pulmonary arterial pressures from those with frank pulmonary arterial hypertension. These reports have suggested that these echocardiographic features might also provide a noninvasive means of determining the level of pulmonary arterial pressure. We designed this study to test the ability of these echocardiographic findings to predict the pulmonary arterial pressure.

Lack of correlation of pulmonary valve echogram and severity of pulmonary hypertension: Our study indicated that mid systolic notching of the pulmonary valve was a specific indicator of severe pulmonary hypertension, but it was of low sensitivity. Other findings tested were neither specific nor sensitive. Furthermore, there was no correlation between changes in echocardiographic pulmonary valve morphology and changes in pulmonary arterial pressure. Thus, one cannot rely on echocardiographic features of the pulmonary valve in assessing the severity of pulmonary hypertension.

The loose correlation between the echographic amplitude of the pulmonary valve *a* wave and the difference between the pulmonary arterial end-diastolic pressure and right atrial peak *a* wave pressure suggests that the latter phenomenon is multifactorial and therefore cannot provide a guide to the magnitude of either single pressure. Further support for this explanation comes from the observation that the diastolic motion of the valve is heavily influenced by the overall motion of other structures of the cardiac base.[4]

Limitations of method: Technical difficulties frequently frustrate echographic imaging of the pulmonary valve and also limit its usefulness as a hemodynamic corollary. In 50 percent of our patients we failed to obtain satisfactory late diastolic and early systolic valve images and in all we failed to identify the point of the valve closure. Because echocardiographic determination of systolic intervals depends on accurate identification of this event,[5] study of these intervals as predictors of pulmonary pressure was not possible.

Originally, we hoped to correlate beat to beat changes with the pulmonary valve *a* wave amplitude and with the exact instantaneous level of the pulmonary arterial pressure. However, the respiratory changes in the am-

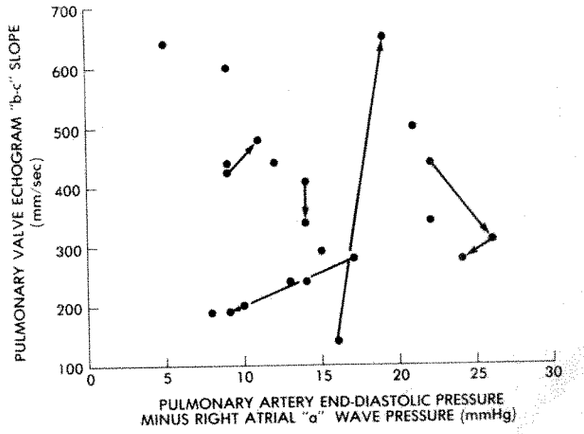


FIGURE 8. Difference of pulmonary end-diastolic pressure and right atrial *a* wave pressure versus pulmonary valve echographic B-C slope. Serial points are connected by **arrows.**

plitude of the pulmonary valve *a* wave relative to respiratory pressure changes were so small that this correlation could not be made. It therefore became necessary in most of our patients to take the average of the pressure and of the echocardiographic values over 10 cardiac cycles. This methodology departs from that of an earlier study.[2] Because our study patients did not show the previously reported degrees of respiratory changes in the pulmonary *a* wave, we speculated that they represented a different population from those of earlier reports. For example, most of our patients were chronically ill and older (59 versus 42[1] and 30[2] years) than patients in previous studies. Thus, this study did not evaluate the possibility that pulmonary valve *a* wave amplitude in a young population is useful in detecting raised pulmonary pressure.

Implications: The morphology of the pulmonary valve echogram is not a reliable guide to absolute or relative levels of pulmonary arterial pressure in patients requiring hemodynamic monitoring. It can therefore serve only as a rough guide to the presence of the more severe levels of pulmonary hypertension.

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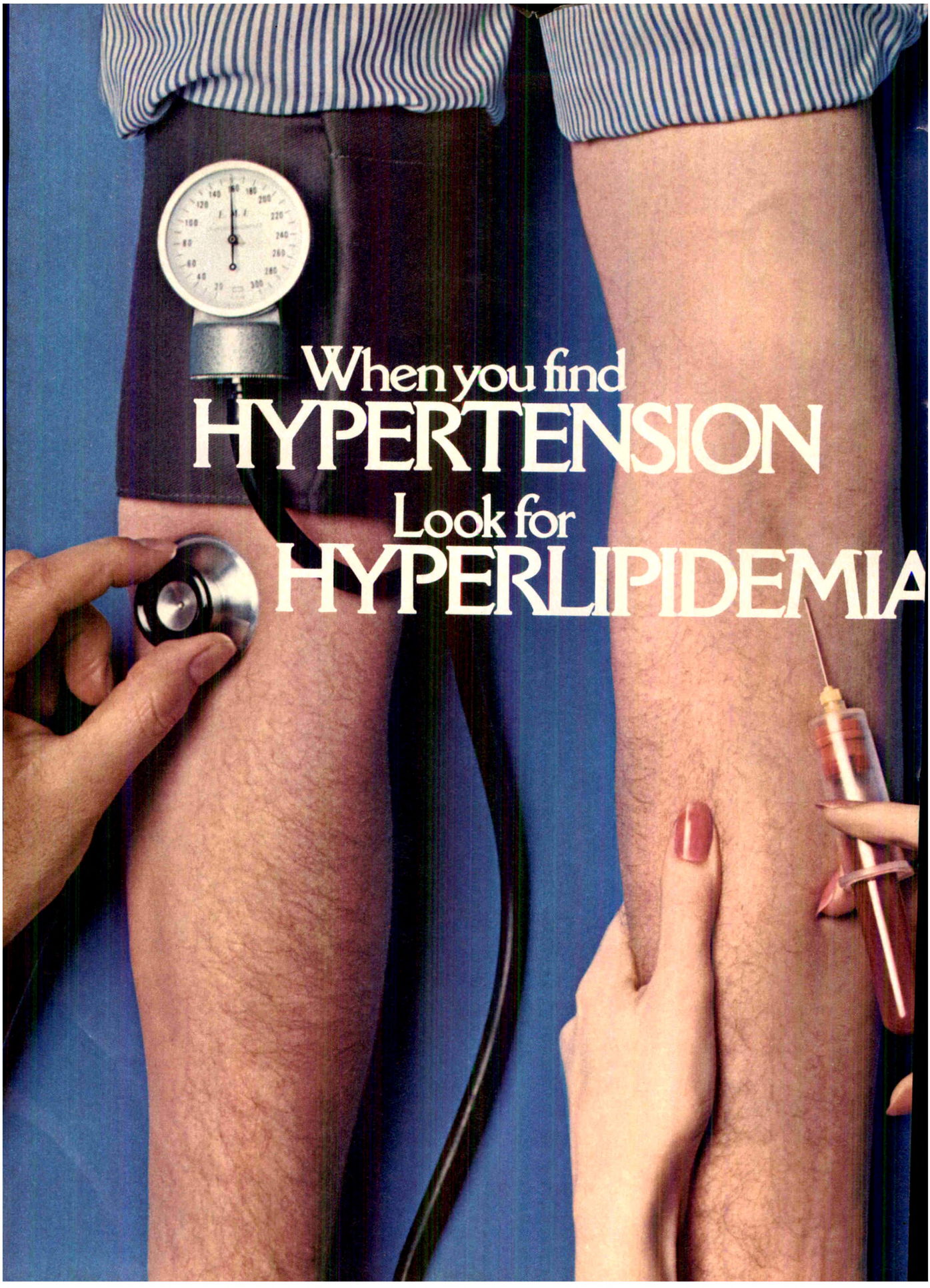
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Type of Hyperlipidemia*	Incidence of Hyperlipidemia	
	Hypertensives (89 subjects)	Normotensives (89 subjects)
Type IIA	9% (8)	7% (6)
Type IIB	6% (5)	3% (3)
Type IV	26% (23)	11% (10)
Total	**41% (36)**	**21% (19)**

*Hyperlipidemia was diagnosed when cholesterol levels exceeded 282 mg% and /or triglycerides were over 177 mg%—cutoff points higher than the usual upper limits of normal.
Adapted from Thomas, G. W., *et al.*[1]

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AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

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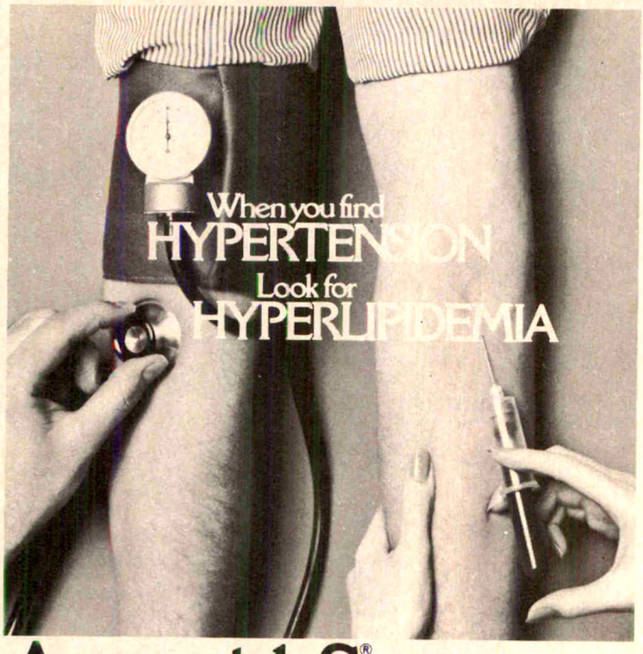
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In more than a decade of use, clofibrate has been generally well tolerated. Major adverse effects are primarily gastrointestinal, with nausea being predominant. Other G.I. reactions include loose stools, flatulence, abdominal distress, and, infrequently, gallstones. Less common reactions include muscle cramping, myalgia, and alopecia. Please see "Important Note" at left and Warning on concomitant anticoagulant usage in prescribing information on following page.

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INDICATIONS: ATROMID-S is indicated as adjunctive therapy in patients who do not respond adequately to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

Administration of clofibrate to mice and rats in long-term studies at eight times the human dose resulted in a higher incidence of liver tumors than in controls. Lower doses were not studied. Although the relevance of this finding to humans is not known at this time, it cannot be dismissed especially since this drug is intended for long-term administration. ATROMID-S should be used only in patients with hyperlipidemia who do not respond adequately to dietary intervention.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long-term administration of a drug of this nature, adequate baseline studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original baseline may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate, bottles of 100.

References: 1. Thomas, G. W., *et al.*: Br. Med. J. *2*:805 (Sept. 24) 1977. **2.** Ahrens, E. H. Jr.: Ann. Intern. Med. *85*:87 (July) 1976. **3.** Council on Foods and Nutrition: J.A.M.A. *222*:1647 (Dec. 25) 1972. **4.** Scheig, R.: Conn. Med. *39*:71 (Feb.) 1975. **5.** Letters to the Editor: Current Prescribing (July) 1977, p. 15. **6.** Fredrickson, D. S., *et al.*, in Holmes W. L., Carlson, L. A., and Paoletti, R. (eds.): Drugs Affecting Lipid Metabolism, vol. New York, Plenum Press, 1969, p. 314. **7.** Brown, H. B., Lewis, L. A., and Page, I. H.: Clin Pharmacol. Ther. *17*:171 (Feb.) 1975. **8.** Gelfand, M. L., and Garbor, M.: Exhibit, American College of Cardiology Meeting, New Orleans, La., Feb. 21-Mar. 1, 1970. **9.** Zelis, R. *et al.*: J. Clin. Invest. *49*:1007 (May) 1970. **10.** Levy, R. I., *et al.*: Ann. Intern. Med. *77*:2 (Aug.) 1972. **11.** Berkowitz, D.: J.A.M.A. *218*:1002 (Nov. 15) 1971. **12.** Lorenzo, E. M. *et al.*: Curr. Ther. Res. *22*:147 (July, Sect. 2) 1977.

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If people can go on diets, so can pacemakers.

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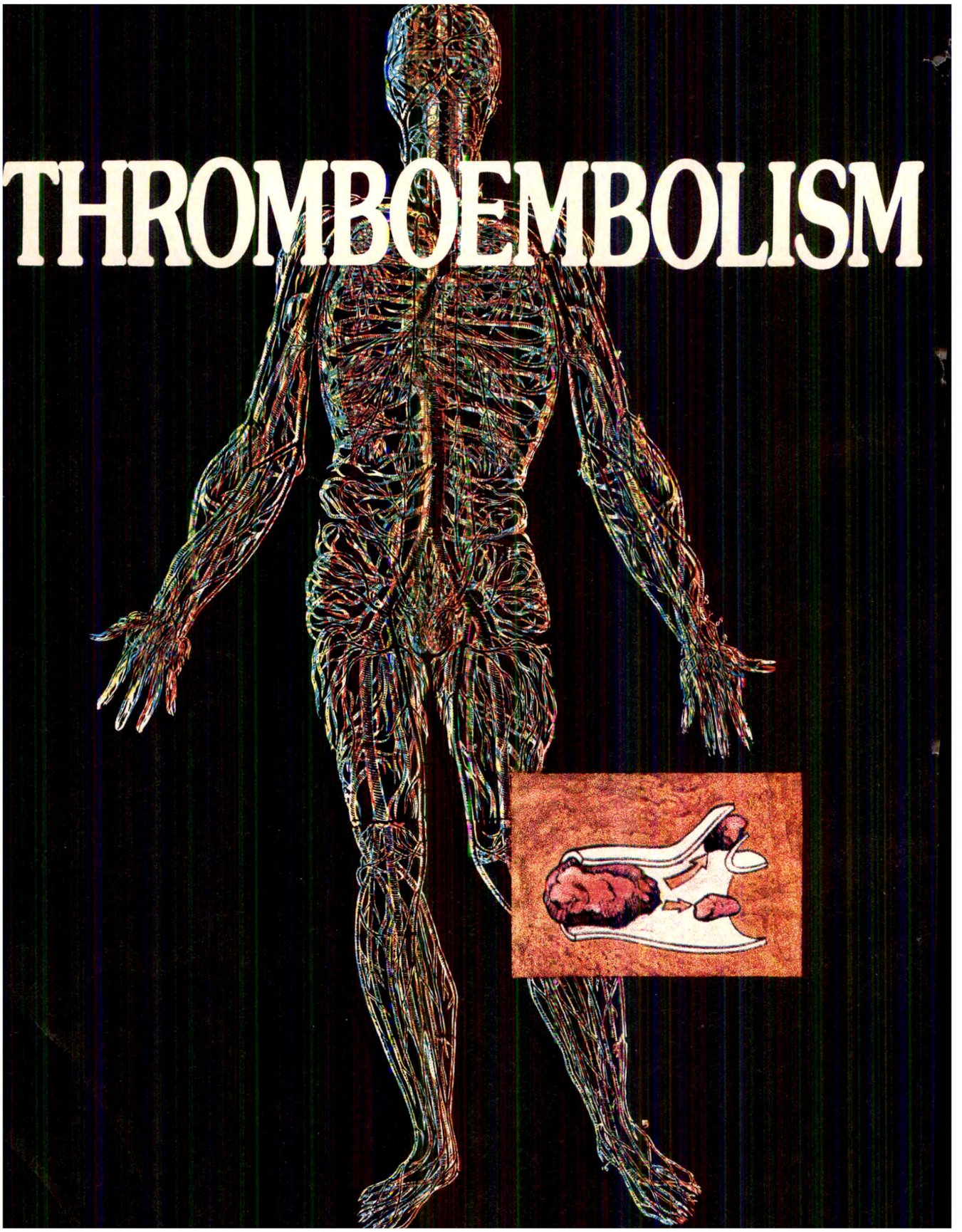
For complete technical data, write Vitatron Medical b.v., P.O. Box 76, Kanaalweg 24, Dieren, The Netherlands. In the United States: Vitatron Medical Inc., One Gateway Center, Newton, MA 02158.



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Vitatron Medical

THROMBOEMBOLISM



COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN®

The oral anticoagulant of choice

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.

Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark; U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy–COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN®.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma, collagen disease; congestive heart failure; diarrhea, elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate, metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid, oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather, prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin-K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN® with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN® may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN®, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN® may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution. 50 mg: Unit consists of 1 vial, 50 mg sodium chloride, 10 mg thimerosal, 0.2 mg; pH is adjusted with sodium hydroxide, accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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CPI'S NEW POROUS TIP LEAD: THE PROBLEM SOLVER

PROBLEM: Endocardial Lead Dislodgement, Causing Threshold Rise or Loss of Capture.

SOLUTION: CPI's New Porous Tip Lead

CPI addressed the problem of lead dislodgement and designed the problem solver: a unique porous electrode. The tip consists of a platinum-iridium screen covering a mesh ball of the same alloy. Optimally-sized fibers give 85-90% porosity so tissue ingrowth knits the tip to the endocardium. Within 24 hours post-implant, the electrode begins its embedment. Clinical studies have demonstrated markedly reduced dislodgement with the porous tip lead. In animal trials, the dislodgement rate was significantly lower than the solid tip control group.[1]

Histologic studies show tissue ingrowth in the acute phase, resulting in a secure electrode-tissue bond chronically, with a noticeably thinner and more structured fibrotic capsule that increases sensing capability.

PROBLEM: An Electrode Tip Must Be Small to Pace Efficiently, but Large Enough to Sense Effectively.

SOLUTION: CPI's New Porous Tip Lead

For pacing the 7.5mm² tip offers reduced current drain, increasing the longevity of constant voltage pulse generators.

For sensing the tip's porosity allows maximum use of the effective sensing area—more than 50mm²—on exterior and interior surfaces. Presence of tissue and fluid within the tip reduces polarization losses. The electrode transmits a larger R-wave, so it offers a sensing advantage.

PROBLEM: Fibrotic Capsule at Lead Tip Can Reduce Chronic Sensing Ability.

SOLUTION: CPI's New Porous Tip Lead

The platinum-iridium mesh fibers are 25μm in diameter, approximating cardiac cell size and thus minimizing tissue reaction.[2] The electrode becomes an integral part of the endocardium. Similar success has been experienced with Dacron fibers of the same size used in artificial heart valves.

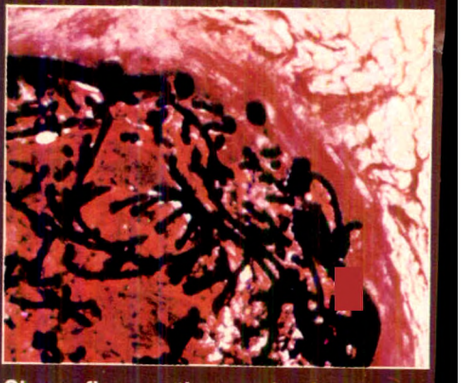
Biocompatible size and quick stabilization mean the electrode causes very little endocardial irritation. Our histologic studies reveal that the fibrotic capsule surrounding the porous tip is significantly thinner than the capsule around a solid tip. The capsule is typically more structured, further indication of this electrode's biocompatibility.

Slimming the fibrotic capsule has significant results—the cardiac signal amplitude and slew rate remain high, so the lead senses reliably in the chronic phase.

Low Dislodgement Rate... Efficient Sensing and Pacing...the Problem Solver from CPI.



Shown 24 hours post-implant, a cross-sectional 100X magnification of the porous tip-canine tissue interface. A fibrinoid collagen capsule has penetrated the outer lattice. Optimally spaced platinum-iridium fibers have allowed electrode ingrowth to begin.



Shown five months post-implant, a cross sectional 100X magnification of the porous tip-canine tissue interface. Dense connective tissue has penetrated the intraelectrode spaces. The fibrotic capsule measures about 300 microns in thickness.

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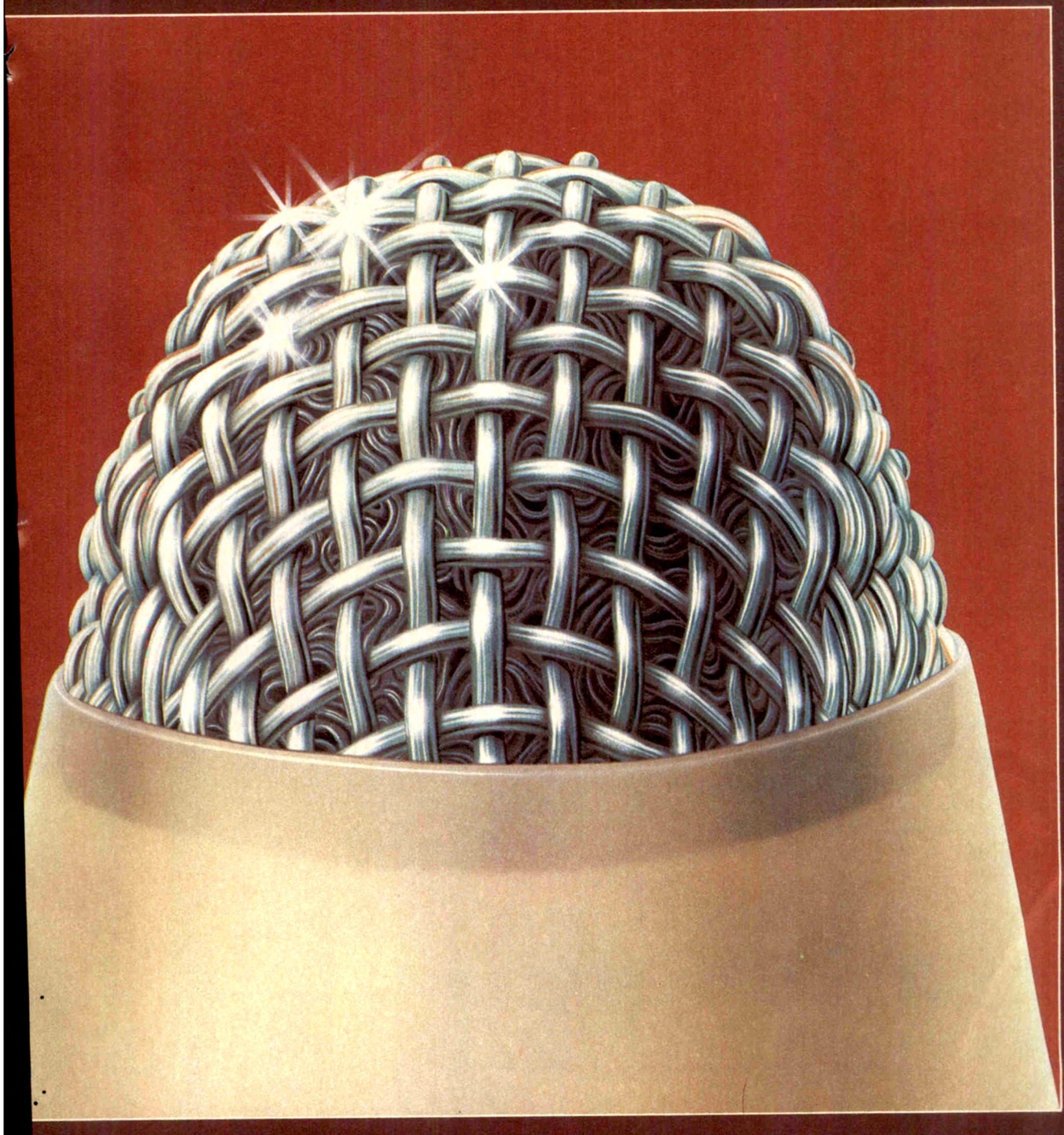
CPI POROUS TIP ENDOCARDIAL LEADS Models 4115, 4116 and 4117 are available in 52, 59 and 85 cm lengths, respectively. All are unipolar, with double-wound conductors of corrosion resistant MP35N nickel alloy. Silicone rubber sheaths the conductors and ends in a flange behind the porous platinum-iridium tip. The outer screen of fibers 40μm in diameter secures the electrode mechanically and assures less traumatic bonding with endocardial tissue. Fibers of the interior mesh are 25μm in diameter to reduce tissue reaction and promote sensing. The unique porous tip is constructed by an advanced bonding technique, which fuses the wire bonds and maintains the integrity of the platinum-iridium electrode without compromising the random configuration.

Cardiac Pacemakers, Inc.
4100 North Hamline Avenue
P.O. Box 43079
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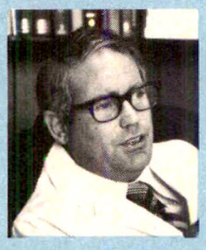
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Inner-View No. 2

A continuing educational series in Nuclear Cardiology



The interview excerpted here was conducted with Glen W. Hamilton, M.D., Chief, Nuclear Medicine Section, Veteran's Administration Hospital, Seattle, Washington. Dr. Hamilton is also an Associate Professor of Medicine, University of Washington School of Medicine.

Q. Of the nuclear cardiology studies available in clinical practice today, which are the most difficult to interpret?

A. Thallium images are probably the most difficult to interpret, and pyrophosphate are probably the next. In about 60% of all abnormal studies, the abnormality is quite obvious. The remaining 40% are quite difficult to read. As the physician gains experience, he will be able to read about half of those with confidence, but about 20% of all thallium studies remain difficult to interpret. Experienced observers will have legitimate disagreement as to whether a given study is normal or abnormal.

Q. Which of these tests are generally the best in the assessment of left ventricular function? Is this also the best study for assessing wall motion?

A. The multiple gated blood pool study yields the greatest clinical information compared to the difficulty of performing the test and, therefore, is the one we use in our clinical practice when we wish to assess a patient's ventricular function. The best study for assessing wall motion is probably the multiple gated study. It is not perfect, in that the right ventricle and the left ventricle overlap in all but the LAO view... but for most laboratories it is the most practical way to assess wall motion.

Q. What studies would you recommend to a nuclear physician or cardiologist beginning nuclear cardiology in a community hospital?

A. I would recommend two studies: multiple gated blood pool studies, and thallium imaging. The ventricular function measurements obtained from multiple gated studies are useful not only in patients who have suspected coronary disease, but also in a wide variety of other patients, such as people with lung disease, older patients who have undetected ventricular dysfunction, or presurgical patients. Clearly, this is going to be the largest volume study, and that's the place where they should start. After doing resting ventricular function studies, they should progress to thallium imaging. Six months from now, there should be enough data available on rest/exercise ventricular function studies using multiple gated imaging to indicate whether this technique is of general usefulness.

Q. Which studies are most difficult to perform?

A. Pyrophosphate studies are obviously the simplest to perform. The multiple gated blood pool study is performed quite simply. However, the equipment required is not present in every laboratory at the present time. Thallium, being a less ideal isotope, is probably the most difficult study, in terms of the technique required to achieve good diagnostic results.

Q. What may be the single most important use of these nuclear cardiology studies in five years?

A. First, I'm confident we will be noninvasively measuring ventricular function in a wide range of patients with various disease states — coronary artery disease, cardiomyopathy, chronic lung disease, valvular heart disease and many others. We will be able to follow these patients, correctly select the optimal time for surgical intervention, and alter medical therapy so that treatment is optimal. There's no question that this will happen. Secondly, if these tests turn out to be quite sensitive for the detection of coronary artery disease in its early presymptomatic stages, it may be possible to alter that disease by various interventions. This could become a very important national endeavor which could have far-ranging effects on health in this country.

Q. How widespread do you see these techniques becoming?

A. The need for studies of ventricular function will be comparable to the need for lung or bone scans. I really expect that most existing nuclear medicine laboratories, and, generally any hospital of two or three hundred beds, will be able to perform ventricular function studies within the next several years.

For the complete transcript of this interview with Dr. Hamilton, write Inner-View, General Electric Company, Medical Systems Division, P.O. Box 414 (Mail Code W-504), Milwaukee, WI 53201.

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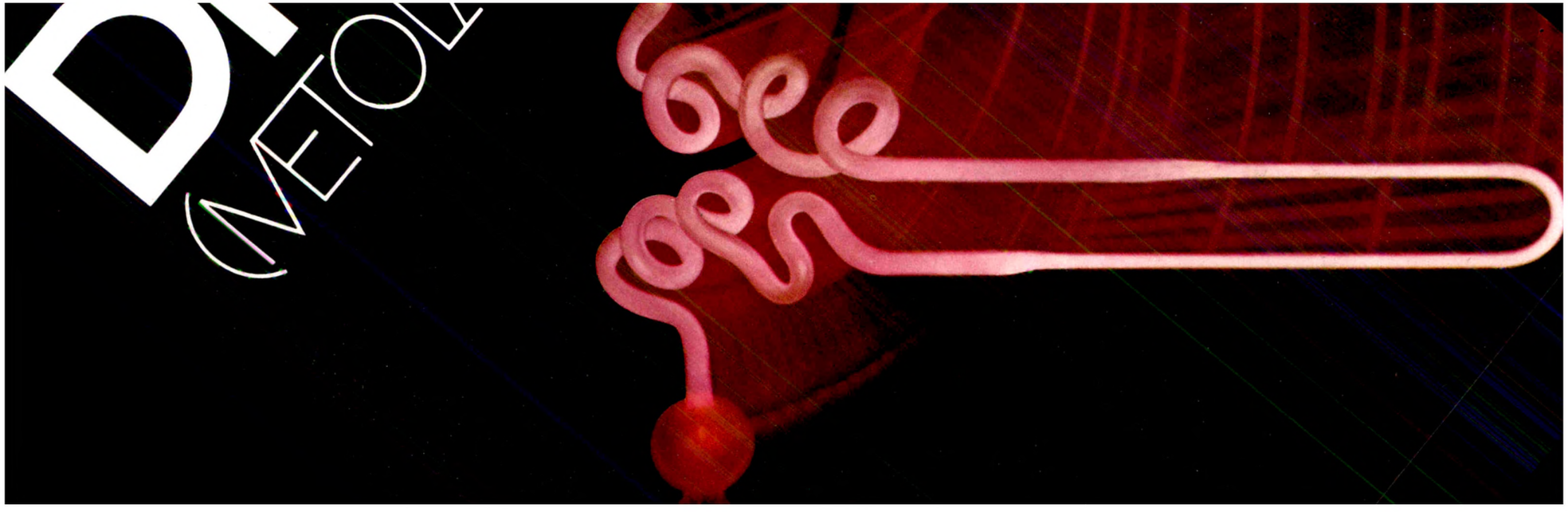
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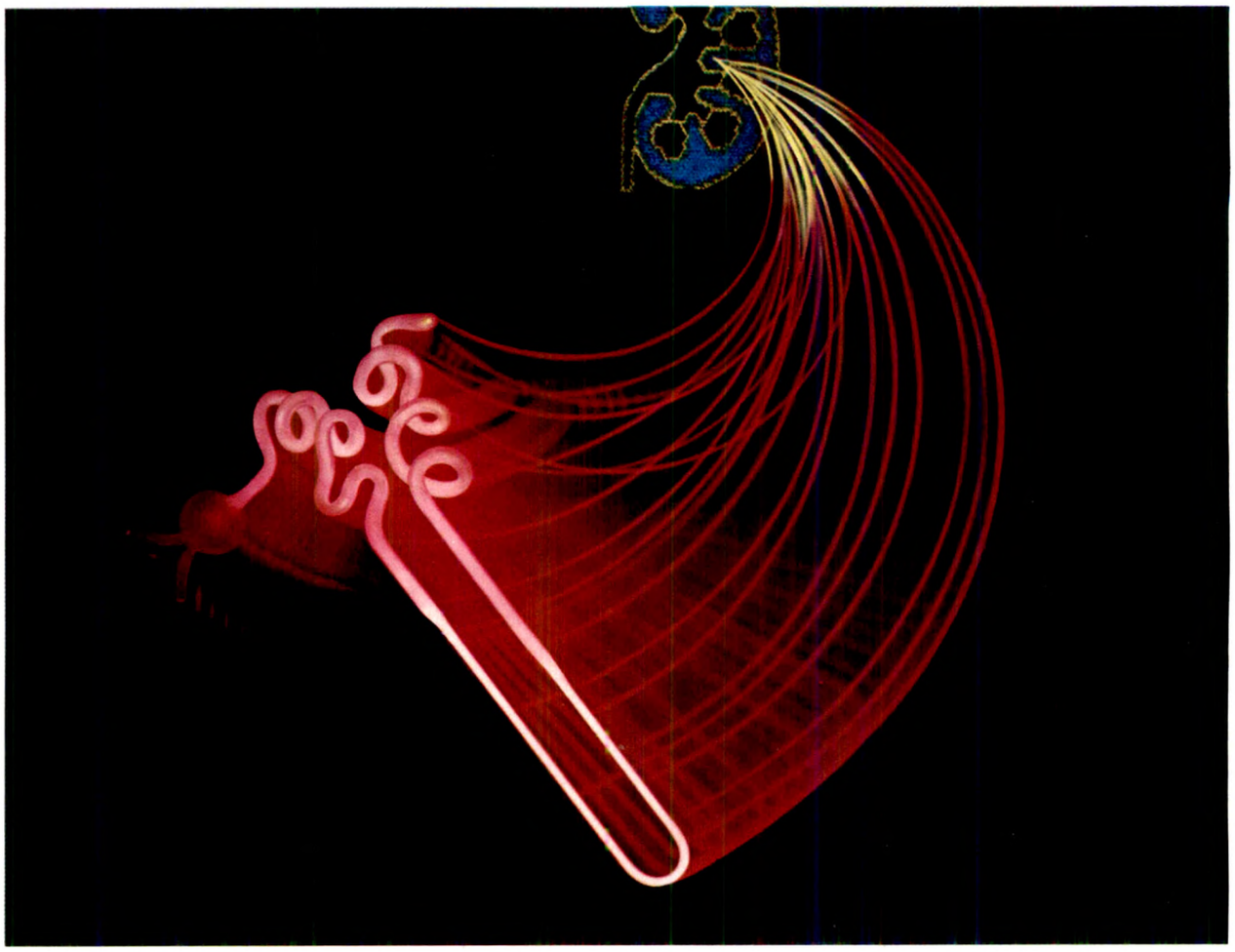


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Maximal Exercise Stress Testing in Evaluation of Arrhythmias in Children: Results and Reproducibility

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To assess reproducibility in evaluating arrhythmias in children, two maximal treadmill exercise tests using the Bruce protocol were performed an average of 3.1 months apart in 19 children aged 5 to 16 years (mean 11) with chronic idiopathic ventricular (Group 1) and supraventricular (Group II) arrhythmias. The performance of each child during the two tests was not statistically different with regard to maximal heart rate achieved or duration of exertion; all but one child achieved expected maximal heart rates. In Group I, eight of nine children with ventricular premature complexes at rest showed suppression of the arrythmia during exercise at similar heart rates on both tests. In one child, ventricular premature complexes were not diminished in either test. One child with accelerated idioventricular rhythm and one with ventricular parasystole had reproducible arrhythmia suppression during exercise. One child with known episodes of ventricular tachycardia had this arrhythmia induced by exercise on both tests. In Group II, five children with supraventricular or junctional premature complexes at rest showed reproducible arrhythmia suppression on exercise, but one unexpectedly manifested ventricular premature complexes and one manifested runs of ectopic atrial rhythm during both exercise periods. Two children with severe sinus bradycardia achieved expected maximal heart rates. One unexpectedly manifested reproducible supraventricular premature complexes after exercise.

Comparison of results of exercise testing with ambulatory electrocardiographic monitoring showed that in four patients testing uncovered arrhythmias not evident on monitoring, whereas in one patient severe sinus bradycardia occurred only during monitoring. These results indicate that maximal treadmill exercise for evaluation of arrhythmias can be performed in children using standard methodology and can yield important data reproducibly.

Exercise testing in children has been applied to a variety of clinical problems: comparison of maximal endurance between normal children and those with structural heart lesions,[1–3] comparison between preoperative and postoperative states in congenital heart disease[4,5] and evaluation of the functional capacity of children with a wide variety of structural heart lesions.[6–10] However, few studies have applied standardized exercise testing to the evaluation of arrhythmias in children,[4–12] although casual exercise is often performed in their clinical evaluation. In adults the use of exercise testing in evaluating arrhythmias is severely limited by lack of reproducibility with regard to arrhythmias,[13–15] but it is not clear whether these data can be extrapolated to children. Additionally, there exist no established standardized criteria on which to base decisions regarding restriction or allowance of strenuous exertion in children with arrhythmias.

To examine the effects of maximal exercise in children with arrhythmias, we performed two separate maximal treadmill exercise tests

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according to the Bruce protocol[16] in a group of 19 children with various known ventricular and supraventricular arrhythmias. In this study we assessed the usefulness and reproducibility of maximal treadmill exercise testing in this group.

Methods

Patient selection: Nineteen children with chronic idiopathic supraventricular and ventricular arrhythmias but otherwise without known cardiac disease were selected as the study group from a large pediatric cardiology clinic population during a 2 year period. All 19 children were asymptomatic apart from their arrhythmias and had been referred specifically for evaluation of an irregular or markedly slow pulse rate. All arrhythmias were confirmed with a resting electrocardiograms before the child's entrance into the study. There were 9 boys and 10 girls whose ages ranged from 5 to 16 years (mean 11 years). No child was physically trained or conditioned. None had evidence of cardiovascular disease clinically by routine laboratory testing, chest X-ray examination or echocardiogram, except for an abnormal frontal plane electrocardiographic axis of −30° in Patient 10 (Table I). No child had a past history or family history of heart disease or evidence of preexcitation, hypoxia, electrolyte abnormalities or thyroid dysfunction. In two children (Patients 10 and 11) cardiac catheterization and ventricular angiographic findings were normal.

The study population consisted of two groups: Group I (Table I) included 12 children with known ventricular arrhythmias. Group II (Table II) included seven children with known supraventricular arrhythmias.

In Group I, nine children had isolated ventricular premature complexes at rest (Patients 1 to 9), and one child each had accelerated idioventricular rhythm (Patient 10), ventricular tachycardia (Patient 11) and ventricular parasystole (Patient 12). In Group II, five children had supraventricular or junctional premature complexes (Patients 13 to 17), and two had episodes of severe sinus bradycardia (Patients 18 and 19).

Exercise tests: All 19 children underwent two separate continuous graded maximal exercise stress tests performed 1 hour to 1 year apart (mean 3.1 months), using the standard Bruce protocol.[16] Equipment consisted of a Quinton Exercise Treadmill, model 18-54, and Marquette series 3500 exercise system recorded with continuous electrocardiographic monitoring by oscilloscope and electrocardiographic printout. Continuous monitoring was started 6 minutes before exercise and was continued up to 20 minutes after exercise. Modified leads II, V_1 and V_5 were employed and were recorded without interruption.

Before exercise, heart rate, blood pressure and a standard 12 lead electrocardiogram and a Frank orthogonal lead (X, Y, Z) electrocardiograms were recorded at rest and during sitting, standing, the Valsalva maneuver and hyperventilation. Blood pressure was monitored throughout the study. In all subjects an attempt was made to achieve maximal duration of exertion. Exercise was terminated abruptly without a "winding down" period, and the patient was placed in the supine position.

Data collection and analysis: Maximal heart rates, blood pressure and the duration of exertion were recorded. Arrhythmias were diagnosed using standard criteria.[17] The frequency and type of arrhythmia and relation to heart rate were noted and recorded. The two exercise tests were performed independently under supervision by different cardiologists, and independent analysis of the data was performed. The results of each test were then compared in each child. The statistical significance, or its lack, of differences in maximal heart rate achieved, duration of exertion, heart rate at suppression or induction of arrhythmias and Q-T intervals for the two tests was determined with Student's t test. Correlation

TABLE I

Group I: Ventricular Arrhythmias

Case no.	Age (yr) & Sex	Arr Pre-Exercise	Exercise 1 Effect	Exercise 1 HR at ↑ or ↓	Exercise 2 Effect	Exercise 2 HR at ↑ or ↓	Ambulatory Monitoring Arr	Effect of Sleep	Rate-Related ↓	HR at ↓ or Max HR (M)	Electrophysiologic Study Effect	Electrophysiologic Study HR at ↓
1	8M	VPC	↓VPC	150	↓VPC	158	VPC	↓	↓	130	. . .	. . .
2	16F	VPC	↓VPC	136	↓VPC	150	VPC	↓	↓	140	. . .	. . .
3	9M	VPC	↓VPC	150	↓VPC	150	VPC	↓	↓	150	. . .	. . .
4	16F	VPC	↓VPC	170	↓VPC	176	VPC	None	No	94M	↓VPC	180
5	8F	VPC	↓VPC	140	↓VPC	140	. . .	. . .	. . .		. . .	. . .
6	16F	VPC	↓VPC	158	↓VPC	158	VPC	↓	No	115M	. . .	. . .
7	16F	VPC	↓VPC	80	↓VPC	88	. . .	. . .	. . .	. . .	. . .	. . .
8	13M	VPC	↓VPC*	160	↓VPC	187	VPC	None	No	125M	↓VPC	170
9	5F	VPC	→VPC	. . .	→VPC	. . .	. . .	. . .	. . .	. . .	. . .	. . .
10	9M	VPC/ AIVR	↓AIVR	136	AIVR	142	VPC/ AIVR	None	No	110M	↓AIVR	150
11	7F	VPC/ VT	NSR/ VT	187/ 160	NSR/ VT	187/ 167	1) VPC, no VT 2) VT†	None	No	1) 120M 2) 124M	↓VPC	182
12	16F	Vent para	↓Vent para	200	↓Vent para	200	Vent para	None	No	110M	. . .	. . .

* One ventricular couplet occurred after exercise.

† Ambulatory monitoring performed in two 24 hour periods.

↓ = suppression (of); → = unchanged; ↑ = increase(d); AIVR = accelerated idioventricular rhythm; Arr = arrhythmias; HR = heart rate (beats/min); Max = maximal; NSR = normal sinus rhythm; Vent para = ventricular parasystole; VPC = ventricular premature complexes; VT = ventricular tachycardia.

coefficients were also determined for the maximal heart rate achieved and duration of exertion in the two exercise tests.

Four children from Group I underwent intracavitary electrophysiologic studies (Table I), and 15 patients had 24 hour ambulatory monitoring at the time of the first exercise test. Intracardiac electrophysiologic studies were performed using standard techniques and standard pacing procedure to try to provoke sustained atrial and ventricular tachyarrhythmias.[17] Electrograms were recorded at filter frequencies of 40 to 500 hertz on an Electronics for Medicine DR-8 research recorder at a paper speed of 100 mm/sec. Normal values for intracardiac conduction intervals in children were taken from previous studies.[18] Twenty-four hour ambulatory electrocardiographic monitoring was performed on an Avionics model 445 Electrocardiocorder, and records were evaluated by a trained nurse using the Avionics 660 Electrocardioscanner. Data derived from these two modes of testing were compared with those obtained during exercise testing with respect to detection of arrhythmias and effect of increased heart rate.

Results

There was no statistically significant difference between the first and second exercise test in any child with regard to mean maximal heart rate achieved (192 ± 22 versus 196 ± 19 beats/min.) (mean ± standard deviation) and duration of maximal exertion (9 26/60 ± 1 35/60 versus 9 37/60 ± 1 36/60 min) (Fig. 1 and 2), although in individual patients there was some variation. Significant S-T segment changes—that is, 1 mm or more of S-T segment depression 80 msec after the J point[16]—did not occur in any of the 19 children. Q-T intervals were normal and varied appropriately with heart rate in all patients. Mean maximal systolic blood pressure was 162 ± 32 mm Hg on the first and 162 ± 26 on the second exercise test. The type of arrhythmia had no influence on any of these variables; all but one child (Patient 7) achieved the maximal heart rate.

Group I: Ventricular Arrhythmias

Exercise tests: Twelve children (Patients 1 to 12) had ventricular arrhythmias before exercise testing. Nine children had isolated ventricular premature complexes (Patients 1 to 9) and eight of these (Patients 1 to 8) reproducibly showed complete suppression of ventricular premature complexes during exercise at a heart rate that was similar in the first and second tests (Table I). Heart rates at the time of arrhythmia suppression ranged from 80 to 170 (mean 142 ± 26) beats/min in the first test and from 88 to 187 (mean 150 ± 28) beats/min in the second test. This difference in heart rate at the time of suppression was significant ($P < 0.05$). In one child (Patient 9) suppression of ventricular premature complexes did not occur despite maximal heart rates of 240 and 200 beats/min, respectively, during the two tests. In all eight children who showed arrhythmia suppression during exercise, ventricular premature complexes returned promptly after exercise when the heart rate fell below the rate of suppression and were increased in frequency for 1 to 3 minutes after exercise. There were no runs of ventricular tachycardia or alteration in coupling interval or wave form of the ventricular premature complexes at the termination of exercise. However, in two patients (Patients 2 and 8) single ventricular couplets were recorded after only one of the two exercise tests.

Ambulatory electrocardiographic monitoring: Ambulatory monitoring for 25 hours in six of the nine children with isolated ventricular premature complexes (Patients 1 to 4, 6 and 8) revealed that, during the day, suppression of ventricular premature complexes occurred in Patients 1 to 3. The suppression occurred in each child at heart rates similar to those that caused arrhythmia suppression during exercise. In the three children whose arrhythmia was not suppressed during ambulatory monitoring, heart rates never approached those that caused suppression during exercise. However, during sleep an entirely different situation prevailed, in that ventricular premature complexes were also suppressed at slow heart rates in a nonpredictable manner in four of the six patients who underwent ambulatory monitoring (Patients 1 to 3 and 6). Diminution

TABLE II

Group II: Supraventricular Arrhythmias

Case no.	Age (yr) & sex	Arr Pre-Exercise	Exercise 1 Effect	Exercise 1 HR at ↑ or ↓	Exercise 2 Effect	Exercise 2 HR at ↑ or ↓	Ambulatory Monitoring Arr	Ambulatory Monitoring Rate ↓ Related	Ambulatory Monitoring HR at ↓ or Max HR (M)
13	9F	JPC	↓JPC	137	↓JPC	146	JPC	No	115M
14	13M	SPC	↓SPC, ect AR*	80	↓SPC, ect AR*	120	SPC SB (HR 35‡)	No	86M
15	11F	SPC	↓SPC	120	↓SPC	122	. . .	. . .	. . .
16	7M	JPC	↓JPC	160	↓JPC	125	JPC	. . .	140
17	11M	SPC	VPC, ↓ SPC	126 82	VPC ↓ SPC	130 84	SPC No VPC	No	110M
18	13M	SB	. . .	. . .	. . .	. . .	SB (HR 37†)	. . .	90M
19	11M	SB	SPC*	. . .	SPC*	. . .	SB (HR 40†) No SPC	. . .	167M

* Arrhythmia occurred after exercise.
† Minimal heart rate.
↓ = suppression (of); ↑ = increase(d).
Arr = arrhythmia; Ect AR = ectopic atrial rhythm; HR = heart rate (beats/min); JPC = junctional premature complexes; Max = maximal; SB = sinus bradycardia; SPC = supraventricular premature complexes; VPC = ventricular premature complexes.

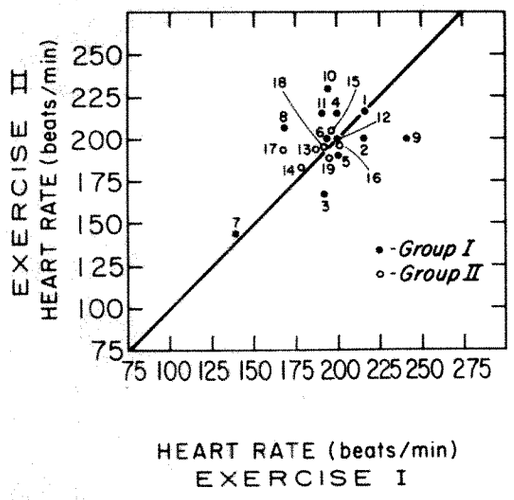


FIGURE 1. Maximal heart rates in all patients in the first (**horizontal axis**) and second (**vertical axis**) exercise tests. The numbers correspond to the patient numbers listed in Tables I and II. $r = 0.498$.

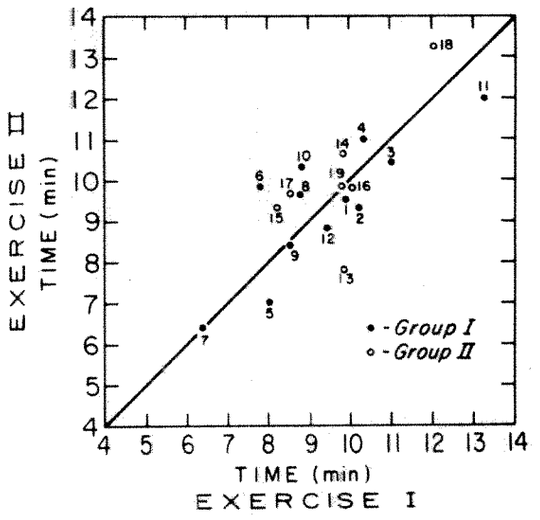


FIGURE 2. Duration of maximal exertion in all patients in the first and second exercise tests. Symbols as in Figure 1. $r = 0.762$.

of ventricular arrhythmias during sleep, perhaps because of a decrease in sympathetic tone, is a well known phenomenon.[19]

One child with ventricular parasystole (Patient 12) had the ectopic rhythm transiently overdriven at rates of 200/min on both exercise tests. We attribute this "suppression" to the rapid rate, which kept the ventricle refractory to depolarizing stimuli from the parasystolic focus. During 24 hour ambulatory monitoring parasystole was never suppressed, even during sleep. Heart rates of 220/min were not observed on ambulatory monitoring. One child with accelelerated idioventricular rhythm (Patient 10) demonstrated reproducible arrhythmia suppression (Table I) on exercise. During 24 hour ambulatory monitoring there was no suppression (during waking or sleeping hours), but the heart rate never approached the rate at which arrhythmia suppression occurred on exercise testing. One child (Patient 11) had ventricular tachycardia, which was induced at similar heart rates (160 and 167 beats/min) (Fig. 3) during both exercise tests. Ventricular tachycardia did not occur during one 24 hour period of ambulatory monitoring but did occur once during a second 24 hour period.

Intracavitary electrophysiologic studies: These were performed in four children (Patients 4, 8, 10 and 11) with ventricular arrhythmias. These studies confirmed that the arrhythmias were indeed ventricular and there was no evidence of accessory pathways functioning in an anterograde or retrograde direction. Ventricular tachycardia could not be provoked by rapid pacing or premature stimulation and intracavitary conduction intervals were normal in all four patients. Suppression of the arrhythmias occurred during atrial pacing at rates similar to those that resulted in arrhythmia suppression during exercise (Table I). More serious ventricular arrhythmias could not be induced by premature atrial or ventricular stimulation or by rapid pacing. The child with ventricular tachycardia on both exercise tests (Patient 11) also had during catheterization runs of spontaneous ventricular tachycardia that were unrelated to pacing.

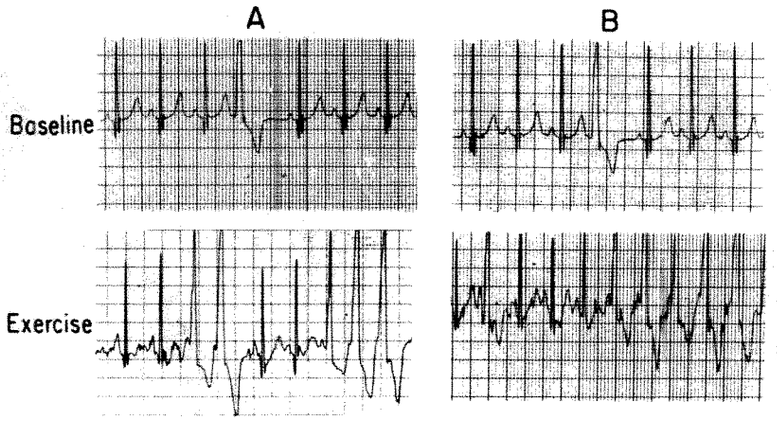


FIGURE 3. Patient 12. Onset of ventricular tachycardia during two separate exercise tests. In the first exercise test (**A**), there were ventricular premature complexes at rest (baseline). At 8 minutes, 40 seconds during the test, when the heart rate was 160 beats/min, there was a ventricular couplet, followed by two sinus beats, and then the onset of a run of ventricular tachycardia. In the second exercise test (**B**) ventricular premature complexes occurred at rest as in **A**, and at 9 minutes, 40 seconds during the test a run of ventricular tachycardia occurred when the heart rate was 167 beats/min.

Group II: Supraventricular Arrhythmias

Seven children (Patients 13 to 19) had ventricular arrhythmias before exercise testing (Table II). Of these, the five with supraventricular or junctional premature complexes (Patients 13 to 17) showed reproducible arrhythmia suppression during both exercise tests, and in three of these suppression occurred at similar heart rates. Supraventricular premature complexes returned in all three children immediately after exercise. Two children with severe sinus bradycardia before exercise (Patients 18 and 19) were able to increase their heart rate significantly during exercise (Fig. 1). Neither child was a conditioned athlete. One of the two (Patient 19) had reproducible ventricular premature complexes after both exercise tests.

Additional arrhythmias: Exercise testing reproducibly elicited several additional arrhythmias in these children from Group II: runs of ectopic atrial rhythm (Patient 14) and ventricular premature complexes during exercise (Patient 17) (both children were thought simply to have supraventricular premature complexes) and supraventricular premature complexes after exercise in a child (Patient 19) thought to have only episodes of severe sinus bradycardia. Also, ambulatory monitoring detected severe unsuspected sinus bradycardia with heart rates of 35 to 37 beats/min during sleep in one child with supraventricular premature complexes (Patient 14).

Response to variations in heart rate: Greater variability in response of arrhythmias to specific increases in heart rate occurred in patients in Group II than in patients in Group I. As noted, suppression of supraventricular or junctional premature complexes occurred at similar heart rates during both exercise tests in only three of the five children. With ambulatory monitoring, heart rates as high as those that suppressed arrhythmias during exercise did not occur in one child (Patient 13), and variation in response between ambulatory monitoring and exercise also occurred in the three other children who underwent monitoring. (Patients 14, 16 and 17). Unlike most of the patients with ventricular premature complexes these children had no suppression of supraventricular or junctional premature complexes during sleep. Intracavitary electrophysiologic studies were not carried out in any child in Group II.

Discussion

Maximal treadmill exercise testing using existing methodology is readily applicable to evaluation of arrhythmias in children. In our study, effects of exercise on a variety of chronic ventricular and supraventricular arrhythmias could be rapidly assessed and, although the number of patients was not large, results were highly reproducible in all 19 children evaluated. Comparison of our results with those of others is difficult because there are no previous studies assessing reproducibility of arrhythmias in children during exercise, although it is known that arrhythmias with exercise are very rare in normal children.[2,4] Adults with ventricular arrhythmias do not respond reproducibly to exercise,[14,15] but the reproducibility of the exercise response to arrhythmias has not been previously evaluated in children.

Importance of heart rate: In this study, heart rate was important in determining the response of ventricular arrhythmias as suggested by the general similarity of heart rates at suppression of ventricular premature complexes in a particular patient during repeated maximal exercise testing, ambulatory monitoring or (when performed) atrial pacing. Also in the two patients with induced ventricular arrhythmias (Patients 11 and 17) heart rates at the time of induction of arrhythmias were similar. The only difference noted was a small but statistically significant increase in heart rate required to suppress ventricular premature complexes from the first to the second test in Patients 1 to 8, which occurred for unclear reasons. Autonomic tone was also important because certain patients with ventricular arrhythmias continuously present below certain heart rates during waking hours had a decrease in arrhythmias at similar or lower heart rates during sleep, when sympathetic tone is markedly decreased relative to parasympathetic tone.[19] However, in other patients ventricular arrhythmias were unchanged during sleep, as were atrial arrhythmias. Also, the response of atrial arrhythmias to specific increases in heart rate was far more variable than that of ventricular arrhythmias.

After cessation of exercise, the frequency of ventricular premature complexes and other arrhythmias increased. Hemodynamic factors, that is, a sudden decrease in venous return and cardiac output coupled with persistence of peripheral vasodilatation and lowered blood pressure, may have played a role. Possibly also differences between the rate of decline in sympathetic tone from that of heart rate after exercise might be important. A gradual winding down rather than abrupt cessation of exercise might have curtailed the transient postexercise increase in arrhythmia, although it would not have served the purpose of the test.

Clinical value of exercise testing: The group of apparently normal children we studied had no evidence of underlying heart disease and were therefore considered to have idiopathic arrhythmias. In spite of the uncertain etiology of arrhythmias in our group, our results demonstrate the importance of complete diagnostic evaluation especially utilizing maximal exercise stress testing in most if not all children with arrhythmias. For ventricular arrhythmias in our group of patients, maximal exercise testing yielded results more rapidly than 24 hour ambulatory monitoring, and in two children ventricular tachycardia and ventricular premature complexes were induced by exercise (Patients 11 and 17). In no case did maximal exercise testing fail to detect ventricular arrhythmias evident on 24 hour ambulatory monitoring. In patients in Group II with atrial arrhythmias (some of which might be considered relatively "minor"), we found ectopic atrial rhythm with maximal exercise testing and previously unsuspected sinus bradycardia with ambulatory monitoring in one patient (Patient 14), ventricular premature complexes induced by exercise in another patient with supraven-

tricular premature complexes (Patient 17), and supraventricular premature complexes in a patient with sinus bradycardia (Patient 19). Thus the finding of certain arrhythmias previously considered benign in an otherwise healthy child may be only part of a more generalized arrhythmia complex and may be sufficient cause for more extensive evaluation, particularly with maximal exercise testing, but also with ambulatory monitoring and, possibly, intracardiac electrophysiologic studies.

Therapeutic implications: Current approaches to therapy of arrhythmias in children are largely empirical because little is known about the natural history or dangers of these arrhythmias. Some patients with ventricular arrhythmias or sinus nodal dysfunction and no other apparent underlying heart disease are subject to sudden death[20,21] and, therefore, it is important to do appropriate complete evaluations and follow up these patients. Whether to allow or restrict exertional activities in a child with arrhythmias is not clear. In the present study of a small group of children we found that maximal exercise testing could either suppress or induce arrhythmias reproducibly. Because of the reproducibility of the test it would appear to be valuable in deciding whether to restrict or allow exertional activities and in assessing the efficacy of antiarrhythmic drugs although there is no evidence that suppression or induction of arrhythmias with exercise indicates overall prognosis.

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Echocardiographic Assessment of Discrete Subaortic Stenosis In Childhood

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The validity of Laplace's relation for assessing peak left ventricular pressure has previously been demonstrated in children with congenital aortic valve stenosis by using the echocardiographically determined end-diastolic h/r ratio (that is, the ratio of mean left ventricular septal and posterior wall thicknesses to half the minor left ventricular cavity axis). This report examines the applicability of this ratio to the preoperative assessment of left ventricular pressure in 17 children with discrete subaortic stenosis. Because the regression equation derived from previously published data on patients with aortic valve stenosis and the present data on children with subaortic stenosis were similar, a pooled estimate of peak left ventricular pressure (LVP) in children with left ventricular outflow tract obstruction is presented: LVP = 312.23 (h/r) ± 28.01 (h/r).

Additionally, the left ventricular outflow tract was measured as the anteroposterior dimension between the first recognizable closure point of the mitral valve and the interventricular septum and expressed as the left ventricular outflow tract/aortic root dimension (LVOT/Ao) ratio. This ratio was lower in patients with subaortic stenosis than in control subjects and was helpful in differentiating patients with mild stenosis from those with more severe stenosis. The prevalence of echocardiographically observed features such as early systolic closure of the aortic valve and fluttering of the aortic valve leaflets could not be correlated with the severity of stenosis. It is concluded that the end-diastolic h/r ratio and the LVOT/Ao ratio are quantitatively useful in the assessment of subaortic stenosis, whereas the commonly present motion abnormalities of the aortic valve are not indicative of the severity of the subaortic lesion.

Anatomic stenosis at the subaortic region may be due to a fibrous membrane, fibromuscular ridge or fibromuscular tunnel in the outflow tract of the left ventricle.[1–3] These anatomic types can be differentiated and their severity assessed by angiographic and hemodynamic studies at cardiac catheterization. In the past various noninvasive techniques have been used to assess the severity of aortic valve stenosis. Principal among these have been clinical findings,[4–6] electrocardiography at rest and at exercise,[7] vectorcardiography[8–11] and phonocardiography. These methods have been directed to the estimation of both peak left ventricular pressure and the pressure difference across the left ventricular outflow tract. Each method has been useful but none has proved consistently reliable.[8,12–14]

Recently, single crystal M mode echocardiography has been shown to be useful in diagnosing discrete subaortic stenosis. Narrowing of the left ventricular outflow tract and motion abnormalities of the aortic valve have been described, although quantitative assessment of the left ventricular outflow tract has not been reported.[15–20] Echocardiographic methods using left ventricular systolic cavity and wall dimensions have been found useful in the estimation of left ventricular pressure.[21–24] In

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an earlier study on congenital aortic valve stenosis we[23] reported a linear relation between the echocardiographically determined end-diastolic $\bar{h}/r$ ratio (ratio of the mean left ventricular posterior and septal end-diastolic wall thicknesses to half the end-diastolic minor axis) and the peak left ventricular pressure as measured at cardiac catheterization.

In this report we present data for quantitative assessment of the left ventricular outflow tract, evaluate the applicability of the end-diastolic $\bar{h}/r$ ratio to estimation of peak left ventricular pressure in children with subaortic stenosis, and examine the prevalence of other echocardiographically observed features suggestive of that diagnosis.

Methods

Patients: Seventeen patients with discrete subaortic stenosis, 1.6 to 16.4 (mean 9.0) years old, were studied with echocardiography and cardiac catheterization. The angiographic diagnosis was membranous obstruction in 5 patients, fibromuscular obstruction in 10 patients and fibroma at the base of the aortic valve in 1 patient; in 1 patient the nature of subaortic obstruction was not clearly seen angiographically. Ten of the 17 patients subsequently had surgery and the angiographic diagnoses were confirmed in all. Patients with asymmetric septal hypertrophy and other forms of cardiomyopathy as well as patients who had previously had cardiac surgery were excluded.

Echocardiographic measurements: Echocardiograms were obtained with a Smith-Kline Ekoline-20 echocardiograph coupled to a Honeywell 1856 strip chart recorder. A 2.25 megahertz transducer was used for larger children and a 3.5 megahertz transducer for small children. All echocardiograms were obtained in a standardized manner so that the left ventricular echocardiogram was recorded at the tip of the mitral valve.

Measurements of the left ventricular end-diastolic and end-systolic posterior and septal wall thicknesses as well as the left ventricular end-diastolic minor axis were made at this site. Septal thickness was measured from the right ventricular to the left ventricular endocardium, and posterior wall thickness was measured from the endocardium to the epicardium. The end-diastolic minor axis was measured at the time of the peak of the R wave of the electrocardiogram. The left ventricular outflow tract was measured as the anteroposterior dimension between the septum and the first recognizable closure point of the mitral valve below the level of the aortic valve. The measurement extended from the anterior edge of the mitral valve echo to the posterior endocardial edge of the interventricular septum echo. Distortion of the left ventricular outflow tract was avoided by the maintenance of parallel alignment between the aorta and the interventricular septum during the echocardiographic sweeps. Because the absolute left ventricular outflow tract dimension varied with the size of the patient, this measurement was normalized by expressing it as a fraction of the end-systolic anteroposterior dimension of the aorta (LVOT/Ao) (Fig. 1). The aortic root dimensions were measured from the outer edges of the aortic wall echo at end-systole. The aortic valve was examined for evidence of early systolic closure or fluttering of the leaflet, or both.

Pressure measurements: The left ventricular peak systolic pressure and pressure difference across the left ventricular outflow tract were obtained at cardiac catheterization within 24 hours before or after echocardiography. All pressure measurements were made before angiography using carefully flushed fluid-filled catheters coupled to a Statham model P23H strain gauge pressure transducer. Cardiac output measurements, made using the Fick technique, ranged from 3.1 to 5.9 (mean 4.5) liters/min per m^2.

A regression equation was developed relating the peak left ventricular pressure as measured at cardiac catheterization to the echocardiographically determined end-diastolic $\bar{h}/r$ ratio. Because this equation was similar to one previously derived from data on 16 patients with congenital aortic valve stenosis, a third equation was developed based on all 33 patients—17 with subaortic stenosis and 16 with valve stenosis. Confidence limits of the echocardiographically estimated left ventricular pressure based on this final equation were calculated using *t* statistics.

Results

The echocardiographic and hemodynamic measurements in 17 patients with discrete subaortic stenosis are presented in Table I. The peak left ventricular pressure ranged between 90 and 220 mm Hg. The peak systolic pressure difference between the left ventricle and the aorta ranged between 10 and 125 mm Hg.

Morphology of the aortic valve: The echocardiographic findings were adequate to evaluate the aortic valve in 15 of 17 patients with subaortic stenosis. In six children the valve appeared normal. Early or mid sys-

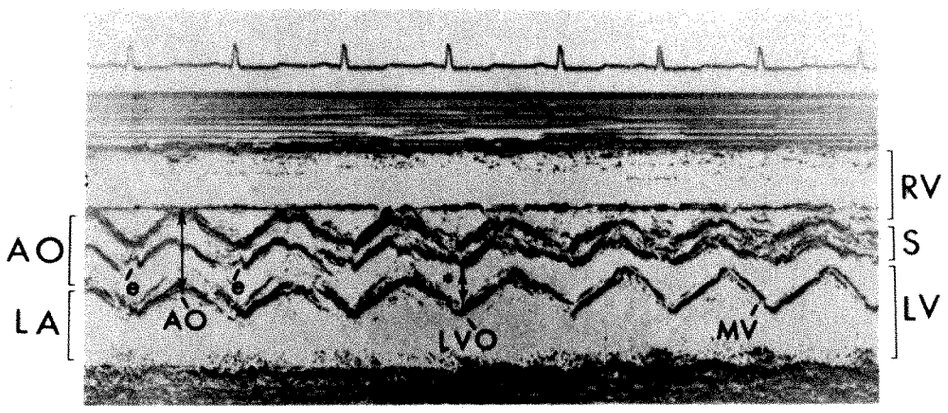


FIGURE 1. Echocardiographic scan from the aorta (AO) to the left ventricle (LV). Note the parallel alignment of the aorta to the interventricular septum (S). The left ventricular outflow (LVO) tract is measured as the anteroposterior dimension (*) between the septum and the first recognizable closure point of the mitral valve (MV) below the level of the aortic valve. The aorta is measured as an anteroposterior dimension between the outer edges of the anterior and posterior vessel wall at end-systole. e = early systolic closure of the aortic valve; LA = left atrium; LV = left ventricle. RV = right ventricle.

TABLE I

Echocardiographic and Hemodynamic Measurements and Derived Variables in 17 Children With Discrete Subaortic Stenosis

Case no.	Age (yr)	BSA (m^2)	Type of Subaortic Obstruction	LVP (mm Hg)	LV-AoΔp (mm Hg)	$\bar{h}$/r	LVOT Dimension (cm)	Ao Dimension (cm)	LVOT/Ao	Flutter	Early or Mid Systolic Closure
1	12.8	1.34	Fibromuscular	160	80	0.50	1.0	2.8	0.36	+	+
2	16.4	1.46	Fibromuscular	135	25	0.45	2.6	3.2	0.81	−	−
3	5.9	0.89	?	110	10	0.35	1.5	2.2	0.68	−	−
4	1.6	0.42	Fibromuscular	220	100	0.62	0.7	1.8	0.39	+	−
5	5.8	0.68	Fibromuscular	130	15	0.52	0.9	1.6	0.60	+	−
6	4.1	0.66	Fibromuscular	143	46	0.45	1.0	2.4	0.42	+	−
7	7.0	0.82	Fibromuscular	130	30	0.39	1.5	2.2	0.68	−	−
8	10.2	1.18	Membranous	90	10	0.31	1.6	2.2	0.73	. . .	. . .
9	4.9	0.80	Fibroma or cyst at base of valve	95	20	0.30	1.2	1.9	0.63	−	+
10	14.3	1.57	Membranous	135	20	0.43	1.3	2.8	0.46	+	+
11	5.8	0.84	Membranous	175	85	0.57	1.2	2.5	0.48	−	−
12	14.3	1.56	Fibromuscular	150	30	0.44	1.7	2.6	0.65	+	+
13	8.3	1.25	Fibromuscular	160	55	0.47	1.3	2.9	0.45	−	+
14	8.5	1.04	Fibromuscular	200	125	0.66	1.4	2.1	0.66	. . .	. . .
15	10.4	1.26	Membranous	110	20	0.41	1.5	2.9	0.52	−	+
16	7.0	0.86	Membranous	140	35	0.43	1.8	2.6	0.69	. . .	. . .
17	12.6	1.29	Fibromuscular	120	10	0.35	2.0	3.0	0.67	−	−

Ao = aorta; BSA = body surface area; $\bar{h}$ = mean of posterior and septal wall thicknesses; LV-AoΔp = peak systolic pressure difference between the left ventricle and the aorta; LVOT = left ventricular outflow tract; LVP = peak left ventricular pressure; r = minor semiaxis (half of the measured left ventricular end-diastolic minor axis).
+ = present; − = absent; . . . = valve leaflets not seen.

tolic closure of the valve was noted in three patients. Coarse fluttering or high frequency vibration, or both, of the leaflets were seen in three patients. In three patients there was early systolic closure as well as fluttering of the leaflets. There was no correlation between the type of angiographically determined anatomic obstruction and these abnormalities. We did not confidently identify anomalous linear echoes of the obstructing membrane in the left ventricular outflow tract of any of our 17 patients.

Quantitation of left ventricular outflow tract (LVOT): The 17 patients with subaortic stenosis had a significant ($P < 0.001$) reduction in the LVOT/Ao ratio (mean = 0.58 ± 0.13 standard error of the estimate) when compared with values in 42 control subjects (0.88 ± 0.06).[25] The 11 children with a left ventricular outflow tract pressure gradient of less than 40 mm Hg (21.4 ± 8.7) had a moderately reduced ratio (0.65 ± 0.10). The six patients with a gradient of more than 40 mm Hg (81.8 ± 29.0) had a significantly ($P < 0.001$) greater reduction in the LVOT/Ao ratio (0.46 ± 0.10).

Estimation of peak left ventricular pressure: The echocardiographically determined end-diastolic $\bar{h}$/r ratio had a linear relation to the peak left ventricular pressure measured at cardiac catheterization for patients with subaortic stenosis similar to the relation we previously demonstrated for patients with aortic valve stenosis (Fig. 2).

The regression equation relating left ventricular pressure (LVP) to the end-diastolic $\bar{h}$/r ratio for the patients with subaortic stenosis was LVP = 314.21 ($\bar{h}$/r) ± 8.95 (standard error of the estimate). In an earlier report we noted a similar relation in 19 children with aortic valve stenosis[22]: LVP = 6 + 298 ($\bar{h}$/r) ± 13.4. When three patients with valve stenosis previously operated on were excluded from this regression analysis, the new equation based on 16 patients was not significantly different from that obtained in the patients with subaortic stenosis: LVP = 312.75 ($\bar{h}$/r) ± 9.75. Accordingly, the two groups of patients were combined and a pooled estimate was made of peak left ventricular pressure in children with surgically untreated left

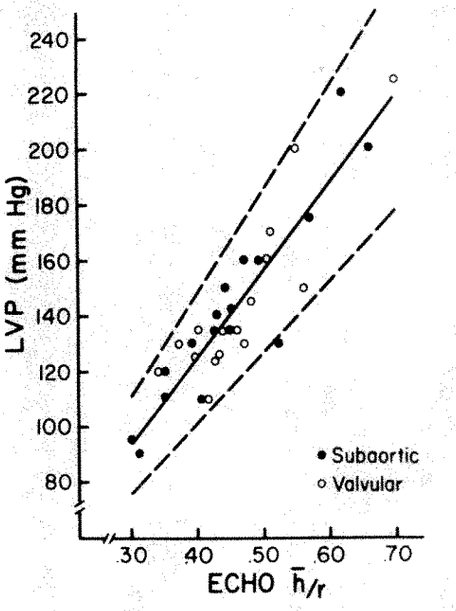


FIGURE 2. Relation between echocardiographically determined left ventricular end-diastolic h/r ratio (ECHO h/r) and left ventricular peak systolic pressure (LVP) at cardiac catheterization in 17 children with discrete subaortic stenosis (**closed circles**) and in 16 children with congenital aortic valve stenosis (**open circles**). The **solid line** indicates the 0.50 probability level. The **dotted lines** define the 0.90 and 0.10 confidence limits.

TABLE II

Range of Standard Error for the Echocardiographically Predicted Left Ventricular Pressure

$\bar{h}/r$	LVP (mm Hg)	Standard Error
0.30	94.0	8.40
0.40	125.3	11.20
0.50	156.6	14.01
0.60	187.9	16.81
0.70	219.3	19.61

$\bar{h}/r$ = ratio of mean of posterior and septal wall thicknesses to minor semiaxis of left ventricle; LVP = peak systolic left ventricular pressure.

TABLE III

Probability (*P*) of Peak Systolic Left Ventricular Pressure Values at Various $\bar{h}/r$ Values

$\bar{h}/r$	LVP (mm Hg)		
	$P = 0.10$	$P = 0.50$	$P = 0.90$
0.30	83	94.0	105
0.35	97	109.6	122
0.40	111	125.3	140
0.45	124	141.0	157
0.50	138	156.6	175
0.55	152	172.3	192
0.60	166	187.9	210
0.65	180	203.6	227
0.70	194	219.3	245

$\bar{h}/r$ = ratio of mean of posterior and septal wall thicknesses to minor semiaxis of left ventricle; LVP = peak systolic left ventricular pressure.

ventricular outflow tract obstruction: LVP = 312.23 ($\bar{h}/r$) ± 28.01 ($\bar{h}/r$).

Because examination of the data indicated that deviations from the estimate tended to be larger when the estimated left ventricular pressure was greater, it seemed appropriate to express the standard error as a proportion of the estimate. Furthermore, because the estimated pressure was directly proportional to the end-diastolic $\bar{h}/r$ ratio, the standard error could be expressed in relation to $\bar{h}/r$ (Table II). Ninety percent confidence limits were calculated using the *t* statistic. Table III presents values of estimated left ventricular pressure at probability (*P*) values of 0.5, 0.10 and 0.90.

Discussion

Echocardiographic abnormalities of the aortic valve: Early systolic closure or fluttering of the valve leaflets, or both, was noted in only half of our patients. Previous workers[18] have described these findings as characteristic of subaortic obstruction, suggesting that the early systolic closure is secondary to alterations in transvalve flow. Our observations suggest that, although these findings are frequently present, their absence in no way precludes the presence of significant subaortic obstruction. In Patient 11 with a measured peak left ventricular pressure of 175 mm Hg and a left ventricular outflow tract pressure gradient of 85 mm Hg there was neither early systolic closure nor flutter. Furthermore, it was not possible to correlate the occurrence of flutter or early systolic closure with any specific type or severity of subaortic stenosis.

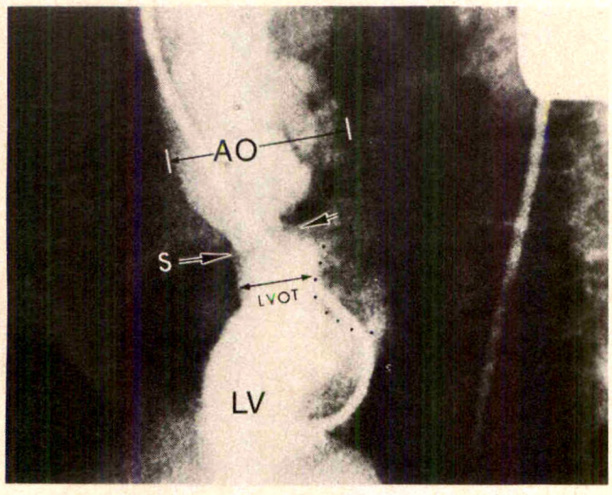


FIGURE 3. Left ventricular angiogram in early systole (left lateral view) in a patient with discrete subaortic stenosis. **Arrows** (S) indicate the level of discrete stenosis and the region of maximal narrowing below the aortic valve. Note the anterior displacement of the mitral valve (**dots**) resulting in systolic narrowing of the left ventricular outflow tract (LVOT) dimension in relation to the aortic root dimension (AO). LV = left ventricle.

Quantitation of the left ventricular outflow tract: Although previous workers[17–19] have recognized echocardiographic narrowing of the left ventricular outflow tract in subaortic stenosis, no quantitation has been reported. Our data suggest that the left ventricular outflow tract is narrowed in these children. They further indicate that the normalized value of left ventricular outflow tract (LVOT), if expressed as the LVOT/aortic root (Ao) dimension ratio, is a useful index that not only identifies patients with subaortic narrowing, but provides some estimate of its severity. Angiographically, the point of maximal narrowing is at the level of the obstructing membrane or fibromuscular ridge (Fig. 3). However, our observations on cross-sectional scanning illustrate that the pliable mitral valve is pulled toward the septum and produces narrowing of the outflow tract along a segment of its length. Echocardiographic measurements at this level permit quantitation of the left ventricular outflow tract using single crystal echocardiography. Although we have not been able to define reliably a discrete obstruction in the outflow tract with the M mode technique, we have consistently noted a significant reduction in the LVOT/Ao ratio. Furthermore, although we were unable to establish a linear relation between this ratio and the left ventricle-aorta pressure difference, we were able to define two groups of patients using this criterion. We suggest that the left ventricular outflow tract measurement in conjunction with the echocardiographically estimated peak left ventricular pressure may be of help in determining the timing and selection of patients for cardiac catheterization.

Estimation of peak left ventricular pressure: In our patients the hemodynamic effect of left ventricular outflow tract obstruction was shown by an increase in

the end-diastolic $\bar{h}/r$ ratio, that is, a disproportionate increase in the left ventricular posterior wall and septal thickness related to intracavitary dimensions. When children with congestive heart failure, asymmetric septal hypertrophy and other forms of cardiomyopathy are excluded, the end-diastolic $\bar{h}/r$ ratio is a useful predictor of peak left ventricular pressure. However, in the practical application of this relation, critical factors to be considered include the techniques of echocardiographic recording and measurement, and variability in the hemodynamic data obtained at cardiac catheterization.

Left ventricular dimensions as assessed echocardiographically vary with the site within the left ventricle at which measurements are made, with phases of the respiratory cycle, and from observer to observer. In our laboratory repeat echocardiographic measurements made by the same observer vary by less than 5 percent. We attempted to minimize variation by making all measurements at the tip of the mitral valve and by averaging the values obtained over five successive beats. In addition, we were especially careful to define clearly the limits of the posterior wall (as distinct from strong echoes from the chordae tendineae) and the margins of the interventricular septum.

From the standpoint of cardiac catheterization there are additional variables to be considered. Left ventricular pressures recorded at catheterization vary with phases of the respiratory cycle and with the level of sedation and do not necessarily represent the day to day averaged peak left ventricular pressure. Nevertheless, any study attempting to correlate noninvasive with invasive data faces such inherent variability to some extent. In view of the inherent variabilities in measurement techniques and the nonequivalency of the invasive versus noninvasive state, we suggest that confidence limits from $P = 0.10$ to $P = 0.90$ are appropriate for the clinical application of the regression equation we derived for estimation of peak left ventricular pressure. Because this method concerns only the estimation of left ventricular pressure, we have deliberately avoided estimating the left ventricular outflow tract-pressure gradient by combining cuff measurements of blood pressure with the echocardiographically estimated left ventricular pressure.

In conclusion, our study demonstrates that in children with subaortic stenosis, the left ventricular outflow tract/aortic root dimension (LVOT/Ao) ratio is significantly reduced relative to that of control subjects, that the end-diastolic $\bar{h}/r$ ratio (ratio of mean left ventricular septal and posterior wall thickness to one-half minor left ventricular cavity dimensions) is a useful predictor of peak left ventricular pressure, and that, while frequently present, previously described echocardiographic abnormalities of the aortic valve are not indicative of the severity of the subaortic lesion.

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Unusual Vascular Anomalies Causing Persistent Pulmonary Hypertension in a Newborn

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A unique case of pulmonary vascular anomalies causing persistent pulmonary hypertension in a newborn is described. The child died 3 days after birth. Necropsy revealed marked hypoplasia of the right and left pulmonary arteries with a normal main pulmonary artery, patent ductus arteriosus, bilateral systemic arteries to the lungs from the abdominal aorta, and partial anomalous pulmonary venous connection. Quantitative morphometric techniques demonstrated slight abnormalities of alveolar development and severe arterial medial hypertrophy with abnormal extension of muscle into small peripheral arteries. Bronchopulmonary development appeared relatively normal in spite of the vascular abnormalities.

Pulmonary hypertension of the newborn or persistent fetal circulation[1] is a syndrome that may result from abnormal pulmonary vasoconstriction[2] or pulmonary arterial medial hypertrophy,[3] but primary lung disease and cyanotic congenital heart disease must always be excluded. We recently encountered an infant who appeared clinically to have persistence of the fetal circulation but instead had a unique configuration of congenital pulmonary vascular anomalies and severe secondary changes of pulmonary arterial hypertension that led to her early death. No intracardiac malformations were present.

In spite of the vascular abnormalities, bronchopulmonary development as assessed with quantitative morphometric techniques was relatively normal. This case is instructive in two respects. First, it shows that bronchopulmonary development may be relatively normal in spite of an aberrant pulmonary vascular supply, and second, the unusual arterial anomalies illustrate an aberration in the normal embryologic sequence of pulmonary arterial development.

Case Report

Clinical History

A 3.52 kg female baby was delivered by elective repeat Caesarian section at 39 weeks' gestation to a 36 year old, gravida 1, para 1 mother. Slight meconium staining of the amniotic fluid was noted at delivery, and the infant's Apgar scores were 6 and 7 at 1 and 5 minutes, respectively. Respiratory difficulty was noted in the delivery room, and oxygen was administered. The first chest radiograph revealed partial collapse of both lungs with mediastinal displacement to the left. Respiratory distress continued, and the child was transferred to Children's Hospital Medical Center at about 36 hours of age.

On physical examination the infant appeared to be of 38 to 40 weeks' gestation. The expiratory phase of respiration was prolonged with audible grunting. Auscultation revealed symmetrical expansion of both lungs with fine diffuse rales. The cardiac apical impulse was shifted slightly to the left of the mid clavicular line. The heart sounds were normal, but a grade 3/6 harsh systolic ejection murmur was heard at the left upper sternal border. The liver was palpable 3 cm below the right costal margin. The chest radiograph revealed increased vascular

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markings in both lung fields with an opacity in the region of the left upper pulmonary lobe. The mediastinum was displaced toward the left. The electrocardiogram revealed normal sinus rhythm at a rate of 155/min, an axis of +150° and right ventricular preponderance, as would be expected at this age.

Cardiac catheterization showed an interrupted inferior vena cava with the azygos vein continuing to the superior vena cava. There was right to left shunting through the foramen ovale and ductus arteriosus (Table I). Partial constriction of the ductus was suggested by a 30 mm gradient between the right ventricle and descending aorta. A right ventricular angiogram (Fig. 1,A and B) revealed a morphologically normal right ventricle that contracted well. The pulmonary outflow tract, pulmonary valve and main pulmonary artery were normal. The right and left pulmonary arteries were severely hypoplastic, long, narrow and tortuous coursing over the superior aspect of the lungs. An aortogram showed bilateral infradiaphragmatic systemic arteries that supplied the lungs from below. The pathways of pulmonary venous return could not be clearly identified, but on levophase the left atrium and left ventricle appeared normal. The impression at that time was that there was persistent fetal circulation with suprasystemic right ventricular pressure as a result of marked hypoplasia of the right and left pulmonary arteries. The infant's condition worsened and she died at age 3 days.

TABLE I

Cardiac Catheterization Data

Site	Oxygen Saturation* (%)	Pressures (mm Hg)
Umbilical artery	67–81	63/48–79/57 (63); 71/54 (60)†
Superior vena cava	62	. . .
Inferior vena cava	67	. . .
Right ventricle	72	107/12; 104/13†
Right atrium	. . .	*A* = 11; V = 8 (11)†

* Obtained in 100 percent oxygen.
† Post-angiography.
Numbers in parentheses are mean values.

Postmortem Methods

The main pulmonary artery was cannulated through the right ventricular outflow tract, and postmortem arteriography was performed by methods previously described.[4] The aorta and systemic vessels to the lungs were also filled by this route through the patent ductus arteriosus. Inflation fixation was performed by previously reported techniques.[4] Lung volumes were determined before and after fixation by water displacement. Proximal bronchial generations were counted under a dissecting microscope and then the peripheral branches of the pathway were reconstructed using step microscopic sections at 300 μ intervals. For microscopic evaluation, three 1 cm^2 sections were taken from both the upper and lower lobes of each lung, and stained with hematoxylin-eosin, elastic Van Gieson and Gomori's trichrome.

Alveolar development: Alveolar development was assessed in three ways: The number of alveoli per cm^2 was calculated,[4] the total alveolar number of each lung was estimated from the formula of Weibel and Gomez[5,6] and radial alveolar counts were performed according to the method of Emery and Mithal.[7]

Arteries: In each section, all the arteries were counted and their external diameter and the thickness of the medial muscular coat measured with a calibrated eyepiece micrometer. Each artery was also landmarked by its accompanying airway. Muscularity was assessed qualitatively by observing whether an artery was completely or partially muscular or nonmuscular and assessed quantitatively by determining percent thickness of the medial muscular coat.[8] Arterial number was expressed as the ratio of alveoli to arteries.[8]

Veins: Since the veins had not been injected, morphometric data were not available, but muscularity was assessed qualitatively.

Necropsy Findings

The inferior vena cava was interrupted above the level of the renal veins; a large azygos vein extended to a right superior vena cava. The visceroatrial situs was normal. There was a normal D-bulboventricular loop, and the pulmonary and aortic roots were normally related. The right ventricular free wall measured 5 to 6 mm and the left ventricular free wall 5 to 5.5 mm. (The upper limit of normal is 4 mm for both ventricles [Table II].) The foramen ovale was probe patent and the ductus arteriosus had a 2 mm luminal diameter.

Pulmonary arteries: The main pulmonary artery was of normal caliber (1.8 cm in circumference) but gave rise to hypoplastic right and left pulmonary arterial branches (each 0.6 cm in circumference). The branches arose posteriorly with the main pulmonary artery continuing as the ductus arteriosus. The right and left pulmonary arteries followed a tortuous,

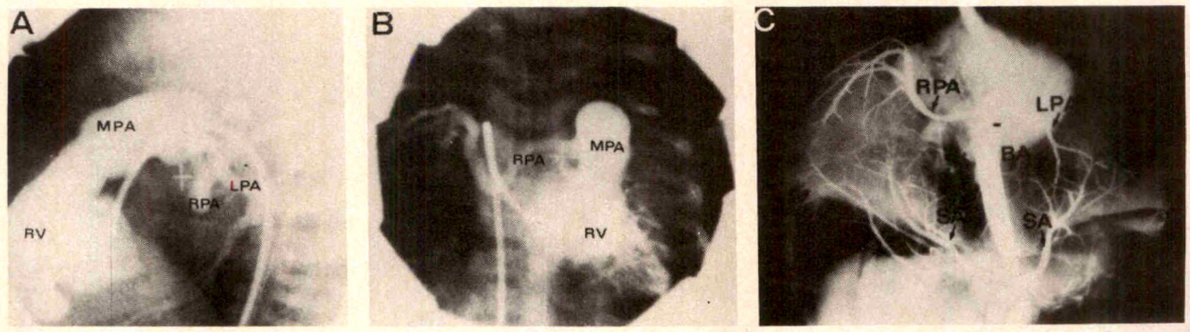


FIGURE 1. A, Right ventricular angiogram in lateral projection showing normal right ventricle and outflow tract, normal main pulmonary artery but hypoplastic right and left pulmonary arteries. **B,** right ventricular angiogram in anterior projection showing poor visualization of left pulmonary artery. **C,** postmortem pulmonary arteriogram after injection of barium-gelatin into the main pulmonary artery (see text). BA = bronchial arteries; LPA = left pulmonary artery; MPA = main pulmonary artery; RPA = right pulmonary artery; RV = right ventricle; SA = systemic arteries.

TABLE II

Organ Measurements and Morphometric Results

A. The Heart

	Present Case	Normal*
Right ventricle (mm)		
Inflow tract	5	3
Apex	3	1–2
Outflow tract	6	3–4
Left ventricle (mm)		
Inflow tract	5	4
Apex	3	2–2.5
Outflow tract	5.5	3.5–4
Pulmonary arterial circumference (cm)		
Main	1.8	1.7–1.8
Left	0.6	1.2–1.3
Right	0.6	1.4–1.5

B. The Lung

	Right Lung	Left Lung	Normal*
Lung volume (ml)	52	36	32 (1 day);64 (3 days)
Lung weight (g)	35	24	. . .
Bronchial generations (post-basal segment) (no.)	. . .	24	24–26
Alveoli/cm^2 (no.)	10,742	12,992	8,277
Alveolar no.	14.4×10^6	7.7×10^6	17.2×10^6 (both lungs)
Radial alveolar counts	5.5	5.5	5.5
Alveolar/artery ratio	22:1	29:1	25:1
Size of arteries (μ) accompanying:			
Terminal bronchioli	98.2 ± 12.3	139 ± 18	118 (87–175)
Respiratory bronchioli	46.4 ± 3	55.6 ± 3.4	92.7 (45–145)
Alveolar ducts	38 ± 2.8	39.2 ± 2.3	65 (60–70)
Alveolar walls	32.1 ± 2.5	36.1 ± 4	32 (25–40)

* Normal values of gross measurements were obtained from hearts of infants of similar weights and gestational age who died of causes unrelated to the cardiovascular and respiratory systems. Normal values of lung volumes and microscopic measurements have been taken from References 4 and 27 to 30 and have been confirmed in our own small series.

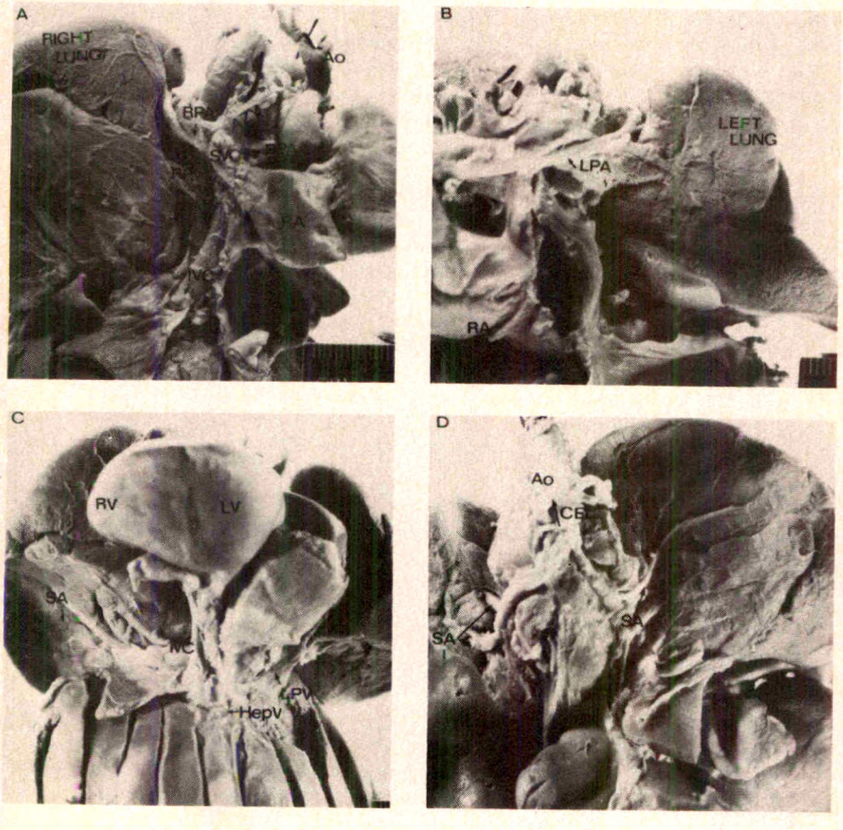


FIGURE 2. A, the left lung and heart have been retracted to the left. The hypoplastic right pulmonary artery is seen as well as the solitary right pulmonary vein, which enters the left atrium (not seen). **B,** view of the hypoplastic left pulmonary artery with the heart retracted to the right. **C,** the cardiac apex has been reflected upward to show the left pulmonary vein draining to a hepatic vein. The systemic arteries to the right lower pulmonary lobe are also seen. **D,** organ block viewed posteriorly with the aorta reflected cephalad and lungs rotated anteriorly to demonstrate entrance of bilateral systemic arteries on the diaphragmatic surface of the lungs. Ao = aorta; AZY = azygos; CEL = celiac artery; HepV = hepatic vein; IVC = inferior vena cava; LPA = left pulmonary artery; LPV = left pulmonary vein; LV = left ventricle; RA = right atrium; RPA = right pulmonary artery; RPV = right pulmonary vein; RV = right ventricle; SA = systemic artery; SVC = superior vena cava.

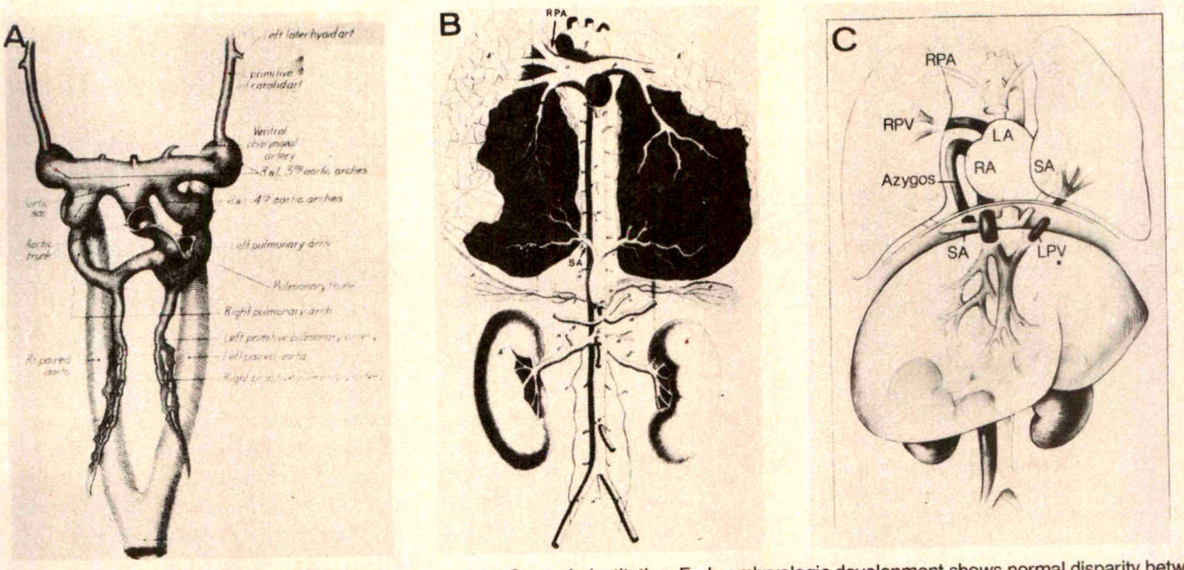


FIGURE 3. A, reproduced from Congdon[23] with permission of the Carnegie Institution. Early embryologic development shows normal disparity between large main pulmonary artery and narrow right and left branch pulmonary arteries resembling the configuration in this case. **B,** reproduced from Maugars[9]. Only the arterial system is shown. The bilateral systemic arteries arising from a single trunk supply the lower pulmonary lobes. Our patient had separate aortic origins of the systemic arteries. **C,** diagram illustrating present case. LA = left atrium; LPV = left pulmonary vein; RA = right atrium; RPA = right pulmonary artery; RPV = right pulmonary vein; SA = systemic arteries.

serpentine course and entered their respective lung at an excessively apical level (Fig. 2, A and B, and 3C). Postmortem pulmonary arteriography demonstrated that the distribution of the pulmonary arteries was limited to the upper lung fields (Fig. 1C). Microscopically, the branches of these arteries were identified coursing normally with the airways.

Systemic arteries to the lungs: Two large systemic arteries arose from the aorta anteriorly in the region of the celiac axis, penetrated the diaphragm and entered the diaphragmatic surface of both lungs (Fig. 2C and 3C). Normal bronchial and intercostal arteries were identified arising from the thoracic aorta. The postmortem arteriogram demonstrates the distribution of both the aberrant and normal systemic vessels to the lungs (Fig. 1C). Microscopically, the large systemic arteries to the lungs were seen in connective tissue septa in the lower lung fields. Their branches passed to assume a position adjacent to terminal bronchioli whence they were distributed to the pulmonary acini (Fig. 4). In the basal portions of the lungs preacinar airways were identified unaccompanied by pulmonary arteries. Both the aberrant arteries and the hypoplastic pulmonary arteries were elastic in structure.

Pulmonary veins: A solitary right pulmonary vein drained from the right hilum to the left atrium (Fig. 2A and 3C). A solitary left pulmonary vein arose from the inferior medial aspect of the left lung, coursed through the diaphragm and drained into a branch of the hepatic vein near the superior surface of the liver, and thence to the right atrium (Fig. 2D and 3C). The left pulmonary vein lumen was very narrow at its junction with the hepatic vein, and a functional obstruction may have been present. Smaller venous channels were present posteriorly draining into intercostal veins that joined the large

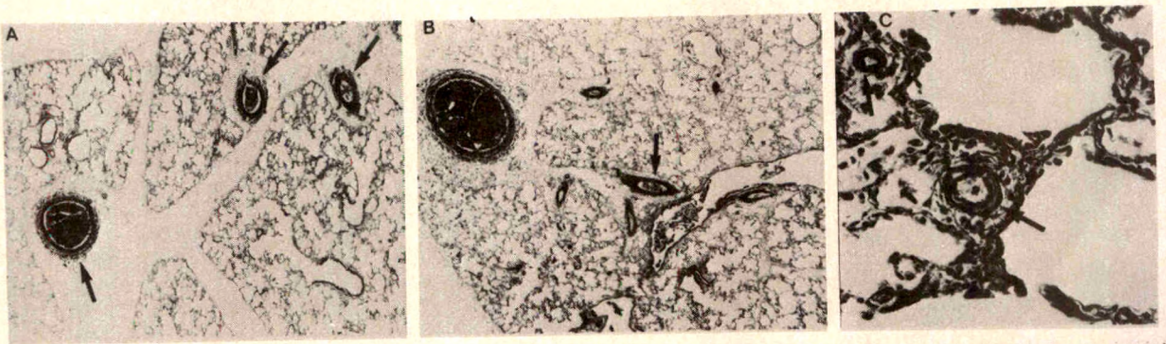


FIGURE 4. Microscopic sections of right lower pulmonary lobe, periphery (elastic van Gieson stain). **A,** elastic systemic arteries are seen in the connective tissue septa (**arrows**). Note the airways without accompanying arteries. (Magnification ×25.) **B,** systemic artery branching to assume position adjacent to terminal bronchiole (**arrow**). Preacinar airways are observed without accompanying arteries. (Magnification ×100.) **C,** alveolar wall artery. Observe abnormal position of muscle in a peripheral artery (**arrow**). (Magnification ×250.)

azygos vein. Microscopically, the intrapulmonary veins appeared normal in number with a slight increase in muscularity. Contrast medium was not present in any venous channels, indicating that no precapillary arteriovenous shunts existed.

Lungs: The lungs were misshapen, but had normal fissures. The right lung was squat, almost globoid in shape. It weighed 35.2 g and had a volume of 52 ml. The left lung had a prominent lingula. It weighed 24 g and had a volume of 36 ml. The main bronchus to each lung entered the lung in an abnormally apical position. Both lungs could be inflated fully. Neither lung had any gross or microscopic evidence of consolidation, scarring or cystic degeneration.

Morphometric Results (Table II, Fig. 5)

Airways and alveoli: Twenty-four bronchial generations were found along the left posterior basal bronchial pathway (normal 24 to 26). Although the total number of alveoli could be accepted as normal, the right lung had twice the number of alveoli of the left, reflecting the smaller volume of the left lung. The disparity between the two lungs indicates at least a relative hypoplasia of the left lung.

Arteries: Arterial concentration was normal, as indicated by normal density of the background haze in the postmortem arteriogram and confirmed by a normal alveolar/arterial ratio for age. The intraacinar arteries, at least at the respiratory bronchiolus and alveolar duct levels, were small. There was abnormal extension of muscle into smaller and more peripheral arteries than normal with complete muscularization as far out as the alveolar wall arteries (Fig. 4). There was a four- to fivefold increase in the thickness of the medial muscular coat in vessels at all levels (Fig. 5). The findings were similar in both lungs whether the arterial supply was by an aberrant systemic or a pulmonary artery.

Discussion

This infant had three major and unique vascular abnormalities: (1) a striking disparity between the normal main pulmonary artery and the hypoplastic right and left pulmonary arteries, (2) bilateral infradiaphragmatic systemic arteries to the lungs, and (3) abnormal venous connections.

Anomalous systemic arteries to the lung: These may be an isolated finding[9–13] or may be associated with a large variety of pulmonary, diaphragmatic and gastrointestinal abnormalities.[14–20] To our knowledge, the case described in 1802 by Maugars,[9] a French medical student, is the only reported instance of a malformation resembling the present case (Fig. 3B).

The lung buds receive an initial systemic blood supply from branches of the aortic sac and dorsal aortas that subsequently regress.[21,22] The definitive branch pulmonary arteries arise directly from the aortic sac, often before the sixth aortic arches are completely formed.[23] These connections are established by the end of the 5th week of gestation. The bronchial arteries arise de novo from the descending aorta between the 9th and 12th weeks of gestation.[24,25] An aberrant systemic artery to the lung may be either a persistent primitive systemic artery or an abnormal bronchial artery. In the former, the origin of the aberrant artery maintains its initial relation to the aorta. With subsequent elongation of the aorta, this artery will arise from the lower thoracic or upper abdominal aorta and course cephalad to enter the lung.[25] This type of aberrant systemic artery is elastic in structure like the normal pulmonary artery and aorta and unlike the bronchial arteries, which are muscular.[26] This histologic resemblance to the normal pulmonary artery may result from similar growth rates because both arteries arise early in embryogenesis and are most likely subjected to similar blood pressures and flow.[25] Both the anatomic and histologic appearance of the

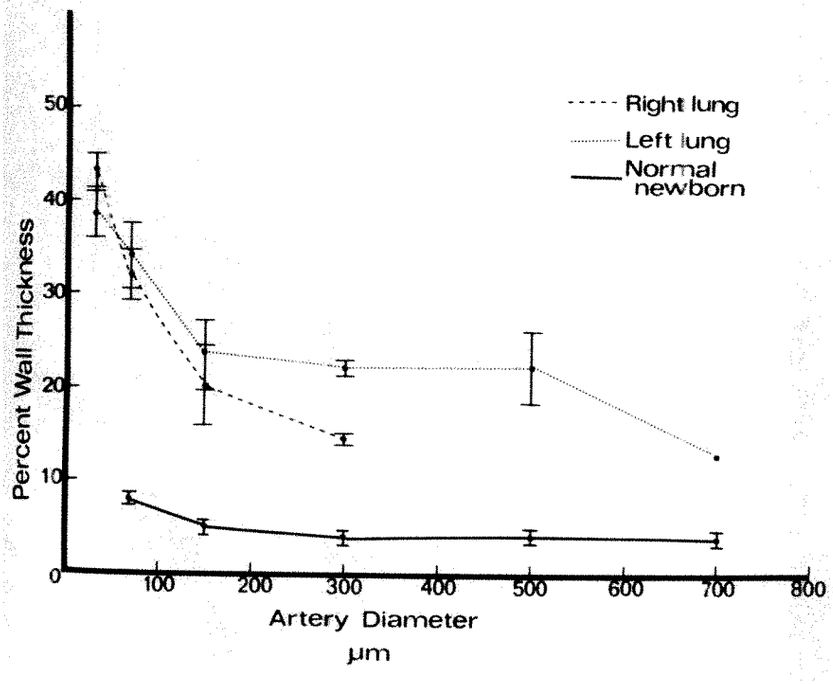


FIGURE 5. Graph showing percent wall thickness as it relates to arterial diameter. Wall thickness in the arteries of both lungs is much greater than normal in arteries of all diameters.

anomalous arteries in this case favor their origin from persistent primitive systemic arteries.

Normal pulmonary artery and hypoplastic branch pulmonary arteries: The main pulmonary artery and the branch pulmonary arteries in our patient strikingly resemble the normal embryonic configuration (Fig. 3A). This primitive appearance may have resulted from failure of the branch pulmonary arteries to grow because a substantial portion of the pulmonary blood flow was carried by the aberrant systemic vessels which had failed to involute. This case strongly supports the theory of segmental derivation of the pulmonary arteries. The main pulmonary artery which, according to this theory, arises from the truncus arteriosus, was of normal caliber and configuration. The abnormalities were confined to the branch pulmonary arteries, which arise initially from the aortic sac and are subsequently incorporated as branches of the sixth aortic arches.[23]

Pulmonary hypertension: Aberrant systemic pulmonary vessels have been implicated as a cause of pulmonary hypertension.[12] Abnormal extension of muscle into smaller and more peripheral arteries with increased thickness of the medial muscular coat has been described in a study of postmortem lungs in infants with persistent pulmonary hypertension of the newborn.[3] These changes have also been seen in patients with pulmonary hypertension due to intracardiac defects,[27] total anomalous pulmonary venous connection[28] and prolonged hypoxia.[29] The morphometric arterial studies in this case suggest antenatal changes of pulmonary hypertension. In the lower lung fields, this was probably the result of the systemic arterial supply. In the upper lung fields where blood flow through the pulmonary arteries was probably reduced as a result of their narrow caliber, one might have expected relative hypoplasia of the arterial musculature as seen in pulmonary atresia.[30] However, arterial musculature was diffusely increased throughout both lungs.

Abnormal venous connections: One could postulate that connections existed between the systemic arteries and the upper lung fields resulting in increased blood flow and pressure in all regions. Alternatively, the presence of solitary pulmonary veins may have caused relatively equal pulmonary venous obstruction to both lungs in spite of the different drainage pathways, and thus it may have been responsible for equal contributions to the arterial muscular abnormality. The anomalous venous connection of the left lung probably did not contribute significantly to the muscular changes in the arteries because the abnormalities were similar in both lungs.

Lung development and growth: In spite of the severe vascular abnormalities and the grossly abnormal appearance of the lungs, there was relatively normal pulmonary development as defined by lung volumes, number of bronchial generations and alveolar development. However, the left lung was hypoplastic in comparison with the right. Because the number of bronchial generations in the posterior basal axial pathway of the left lung was normal, alveolar growth appears to have been impeded. The bronchial tree develops its full complement of branches by the 16th week of gestation[4]; therefore, the hypoplasia of the left lung appears to have resulted from an insult occurring after that time. Because the infant died when she was only 3 days old, reduced postnatal alveolar growth could not account for the smaller size of the left lung. If normal pulmonary vascular development is essential to bronchopulmonary development, one would have expected more severe lung abnormalities reflecting interference with lung growth at a point earlier in gestation than was present in this case.

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Peak Left Ventricular Systolic Pressure/End-Systolic Volume Ratio: A Sensitive Detector of Left Ventricular Disease

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The purpose of this study was to evaluate peak pressure/systolic volume ratio as a detector of cardiac disease. To validate that tracings obtained through fluid-filled catheters were accurate for this purpose, in 35 patients left ventricular pressure-volume loops were constructed from tracings recorded with a micromanometer-tipped angiographic catheter. Comparisons were made between the peak ratio of left ventricular pressure to volume (E_{max}) using the micromanometer-tipped angiographic catheter and the ratio between peak left ventricular pressure before angiography and end-systolic volume during angiography (peak pressure/systolic volume ratio) using the fluid-filled lumen of the same catheter. The relations of E_{max} and that of peak pressure/systolic volume ratio to ejection fraction were similar and curvilinear. Peak pressure/systolic volume ratio was approximately 10 percent higher than E_{max}, with a correlation coefficient between 0.99 of the two ratios. Therefore, peak pressure/systolic volume ratio, which is easily obtained in clinical practice, can be used instead of E_{max}.

Retrospective analysis of the peak pressure/systolic volume ratio and ejection fraction was made from routine diagnostic catheterization data obtained using fluid-filled catheters in 115 subjects, of whom 17 were normal, 60 had coronary artery disease without asynergy, 23 had aortic valve disease and 15 had mitral valve disease. In subjects with a normal ejection fraction (more than 60 percent) the peak pressure/systolic volume ratio separated those groups with a diseased heart from those with a normal heart. Those with a diseased heart had a greater end-systolic volume than normal subjects. Thus, the peak pressure/systolic volume ratio is more sensitive than ejection fraction in detecting subtle changes in myocardial function in human beings.

Studies of isolated heart muscle reveal that during isotonic contraction the peak force generated for any given preload approximates the force generated by an isometric contraction at the same length. The relation of force to initial length appears nearly linear in the physiologic range.[1-3] In the isolated, supported, isovolumically contracting canine left ventricle, pressures generated from different initial volumes also fall along a straight line. Furthermore, in ejecting hearts, the ventricular pressure at end-systole falls along the same isovolumic pressure line.[4] The peak ratio of ventricular pressure to volume (E_{max}), which occurs near the end of systole in isolated dog hearts, appears to be independent of afterload and affected minimally by preload[5] and thus can be used as an index of contractility. Published studies[6] have suggested the usefulness of this measurement in human beings. The ejection fraction, which is the ratio of stroke volume to end-diastolic volume, has been useful for sequentially following up ventricular pump function as well as for predicting the outcome of cardiac surgery.[7] However, diseased hearts can have an ejection fraction within the normal range. It is possible that E_{max}

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or an end-systolic pressure/volume ratio might prove to be more sensitive than ejection fraction for detecting abnormalities in those hearts. The peak systolic pressure/end-systolic volume ratio should be similar to E_{max} because peak systolic pressure and the ventricular pressure when ejection ceases are virtually identical.[8]

The purpose of this investigation was to study the sensitivity of the end-systolic ventricular pressure/volume relation to determine whether this ratio could separate diseased from normal hearts more clearly than the ejection fraction. To simplify the measurement, we validated that the maximal value for the ratio of left ventricular pressure and volume (E_{max}) during systole, which was determined using intracardiac pressure measurements during ventriculography, was similar to the ratio between peak left ventricular pressure measured just before angiography and end-systolic volume measured during angiography (peak pressure/systolic volume ratio). It was then demonstrated that peak pressure/systolic volume ratio was more effective than ejection fraction in separating groups of patients with heart disease from normal subjects. In this study E_{max} was not corrected for zero pressure.[4]

Methods

Procedure: After giving fully informed consent, 35 patients underwent left heart catheterization by way of a femoral arterial puncture using a no. 7F PC 471 Millar micromanometer-tipped angiographic catheter (Mikro-Tip Transducer, Millar Instruments, Inc., Houston, Texas). The transducer, which was first submerged in a lukewarm heparinized 5 percent glucose solution for balancing and calibration, was connected to a Millar model TC 160 transducer control unit and an Electronics for Medicine pressure amplifier, model V2203. The fluid-filled lumen of the PC 471 catheter was connected with a Statham P23db transducer and an Electronics for Medicine pressure amplifier, model V2203. The Mikro-Tip and P23db transducers were calibrated, using a mercury manometer, to have the same sensitivity. Using a Phillips cesium iodide 9 inch image (23 cm) intensifier, cineventriculography at 50 frames/sec was performed in the 30° right anterior oblique view using Renografin-7® dye (40 to 45 ml) injected at 36.3 kg/cm^2 at 12 to 15 ml/sec. In some patients a second angiogram was performed after sublingual nitroglycerin. During cineventriculography, left ventricular pressure and each cine frame number were recorded on photographic paper at 100 mm/sec using 0.02 second time lines (Electronics for Medicine VR 12 multichannel recorder). The pressure tracing and each cine frame number were also recorded on the cine film (Electronics for Medicine model V4290) for each angiographic frame. In these 35 patients peak systolic pressure was recorded through the fluid-filled lumen of the Millar PC 471 catheter immediately before angiography, and it averaged 0.7 percent higher than the peak ventricular pressure recorded during angiography using the Mikro-Tip transducer. This measured difference was not statistically significant. The pressure values before angiography were 125 ± 42 mm Hg (mean ± standard deviation) and 126 ± 40 for peak pressure during angiography.

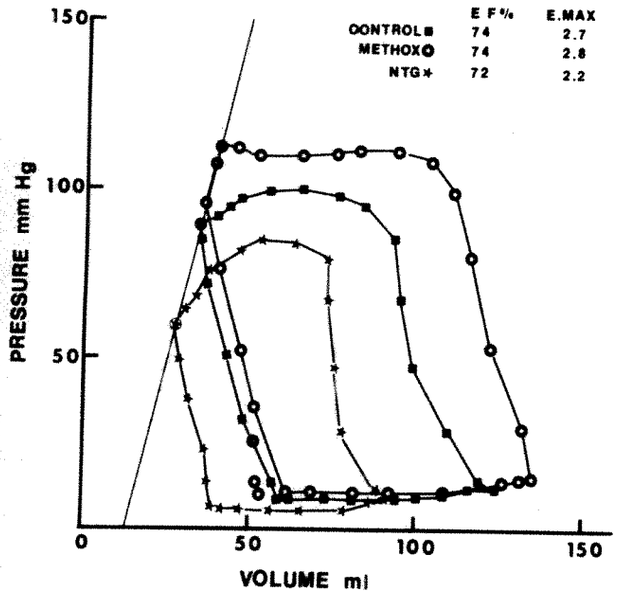


FIGURE 1. The left ventricular pressure/volume relation in one patient with three different loading conditions—the control state and after administration of methoxamine (METHOX) and nitroglycerin (NTG). E F = ejection fraction; E. MAX = peak ratio of ventricular pressure to volume.

Measurements: Frame by frame ventricular volumes were determined by the area-length method with the aid of a light-pen tracer (Conrac) and an Electronics for Medicine computer system, model CLC-1, VVC mode.[9] After identifying the cine frame number from the pressure recording, the ventricular pressure corresponding to the particular cine frame volume was measured and the ventricular pressure-volume loop constructed. In these hearts we calculated the ratio of peak left ventricular pressure before ventriculography to end-systolic volume (peak pressure/systolic volume ratio), the highest value for the ratio of ventricular pressure to systolic volume (E_{max}) during ventriculography and the ejection fraction.

Retrospective analyses: An additional retrospective analysis of peak pressure/systolic volume ratio and ejection fraction was carried out in three groups of patients from our catheterization laboratory. The ventricular pressures were determined from the fluid-filled catheters. The groups consisted of 60 patients with coronary artery disease, 23 patients with aortic regurgitation or aortic stenosis plus regurgitation and 15 patients with mitral valve disease. The control subjects consisted of 17 patients who had a normal electrocardiogram, normal left ventricular end-diastolic pressure, normal coronary arteriogram and normal ejection fraction. Patients who had ventricular dyskinesia or severe hypokinesia were excluded from all analyses. Comparisons between individual groups were made using a Student's t test.

Results

Figure 1 shows representative pressure-volume loops from one normal subject. Three ventriculograms were obtained at different levels of preload and afterload. Methoxamine was used to increase and nitroglycerin to decrease preload and afterload. In this patient the peak left ventricular systolic pressures during the control state and after nitroglycerin were slightly higher than the end-systolic ventricular pressure. After methoxa-

mine, peak and end-systolic pressures were the same. This figure demonstrates that the peak ratios of ventricular pressure to volume (E_{max}) were relatively stable under the three different loads.

Peak pressure/systolic volume ratio versus E_{max}: Peak systolic pressure with the fluid-filled catheter just before angiography averaged 111 ± 4 mm Hg and the end-systolic pressure during angiography was 103 ± 4 (mean ± standard error) ($P > 0.05$; no. = 50). This finding suggests that the peak pressure/systolic volume ratio should be close to E_{max}. Figure 2 shows the values for the peak pressure/systolic volume ratio compared with E_{max} in 50 examinations. The relation is positive and linear, with a correlation coefficient of 0.99. The value of peak pressure/systolic volume ratio is approximately 10 percent higher than E_{max}.

Figure 3 shows both E_{max} and the peak pressure/systolic volume ratio plotted against ejection fraction. The two curves are similar. When ejection fraction is within the normal range of greater than 60 percent, E_{max} and peak pressure/systolic volume ratio vary widely. Therefore, similar information can be derived from the peak pressure/systolic volume ratio and E_{max}. To obtain E_{max} in human hearts a high fidelity catheter-tipped micromanometer angiographic catheter or two catheters are necessary as well as construction of the pressure-volume loop. Therefore, peak pressure/systolic volume ratio may be more practical for use in clinical practice.

Peak pressure/systolic volume ratio versus ejection fraction: Figure 4 shows the plot of peak pressure/systolic volume ratio versus ejection fraction in the patients subjected to retrospective analysis. As predicted, the relation was curvilinear. When ejection fraction was less than 40 percent, the value for peak pressure/systolic volume ratio was less than 1. In patients with an ejection fraction greater than 60 percent, peak pressure/systolic volume ratio ranged between 1 and 5. Normal hearts tended to have higher values for peak pressure/systolic volume ratio. This basic relation was not altered when end-systolic volumes were normalized for body surface area.

To test the sensitivity of peak pressure/systolic volume ratio in detecting disease, hearts with ejection fractions over 60 percent in each disease category were analyzed and compared with findings in the normal group. This sub group consisted of 17 normal subjects, 30 patients with coronary artery disease, 5 with mitral valve disease and 10 with aortic stenosis and aortic regurgitation, 5 of whom had predominant aortic stenosis and 5 who had predominant aortic regurgitation. In patients with aortic stenosis the mean gradient across the aortic valve was 38 ± 20 mm Hg (standard deviation).

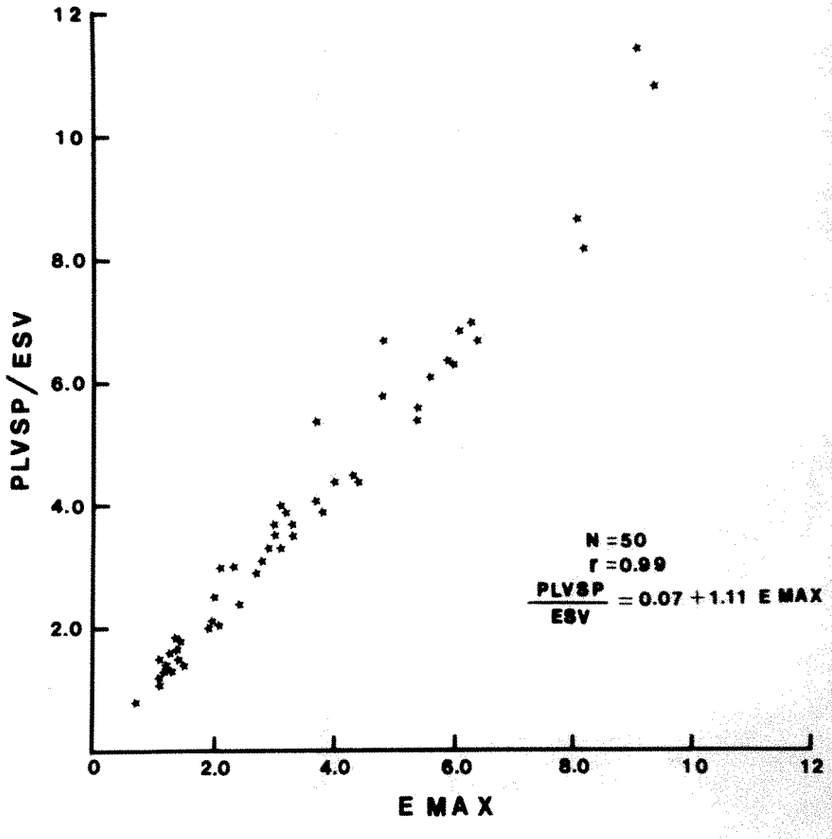


FIGURE 2. Relation of peak left ventricular systolic pressure/end-systolic volume (PLVSP/ESV) ratio to E_{max} in a group of 50 patients. N = number of patients; r = correlation coefficient.

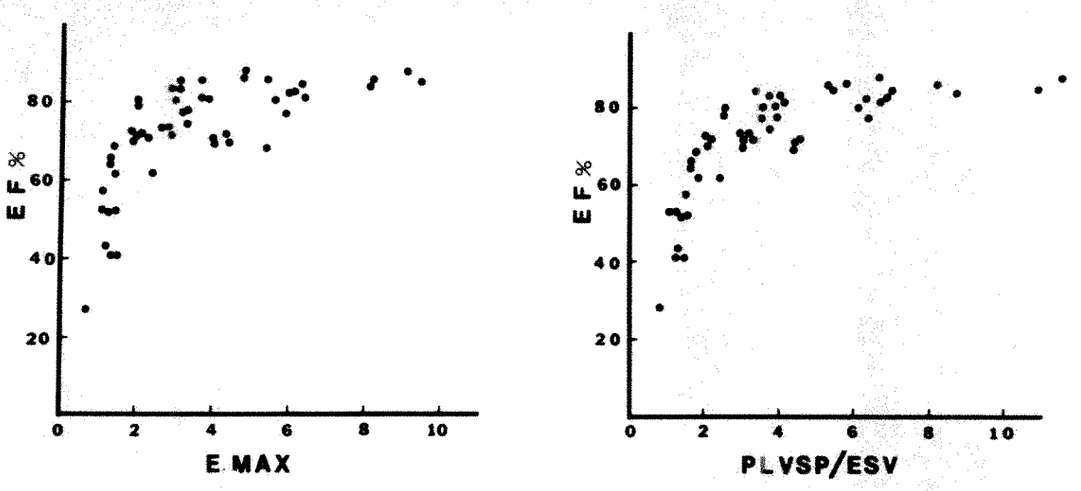


FIGURE 3. Relation of ejection fraction (E F) to E_{max} and PLVSP/ESV.

Figure 5 shows the similarity of the ejection fraction in each patient category. Peak pressure/systolic volume ratio was significantly higher in the normal subjects than in those with a diseased heart ($P < 0.001$). Figure 6 shows that the higher peak pressure/systolic volume ratio in the normal hearts was primarily due to a smaller end-systolic volume. Both end-systolic volume and peak left ventricular pressure were higher in the presence of aortic valve disease than in the normal heart. The increased peak left ventricular systolic pressure is probably not due to increased contractility; it is more likely that it reflects hypertrophy and hyperfunction on the basis of chronic pressure overload. On the other hand, the larger end-systolic volume in aortic valve disease might represent a decreased inotropic state.

Discussion

The value of any new test in clinical medicine depends on the simplicity of its measurement and on its sensitivity compared with other established tests. The ejection fraction is widely accepted as a useful measure of ventricular performance. Our study demonstrates that a simple measure, peak pressure/systolic volume ratio, can detect abnormal ventricular function in patients with cardiac disease while they still maintain a normal ejection fraction. Thus, this ratio appears to be more sensitive than the ejection fraction.

Peak pressure/systolic volume ratio as an index of contractility: The logic for using the value peak pressure/systolic volume ratio stems from the evidence that it reflects the peak ratio of ventricular pressure to

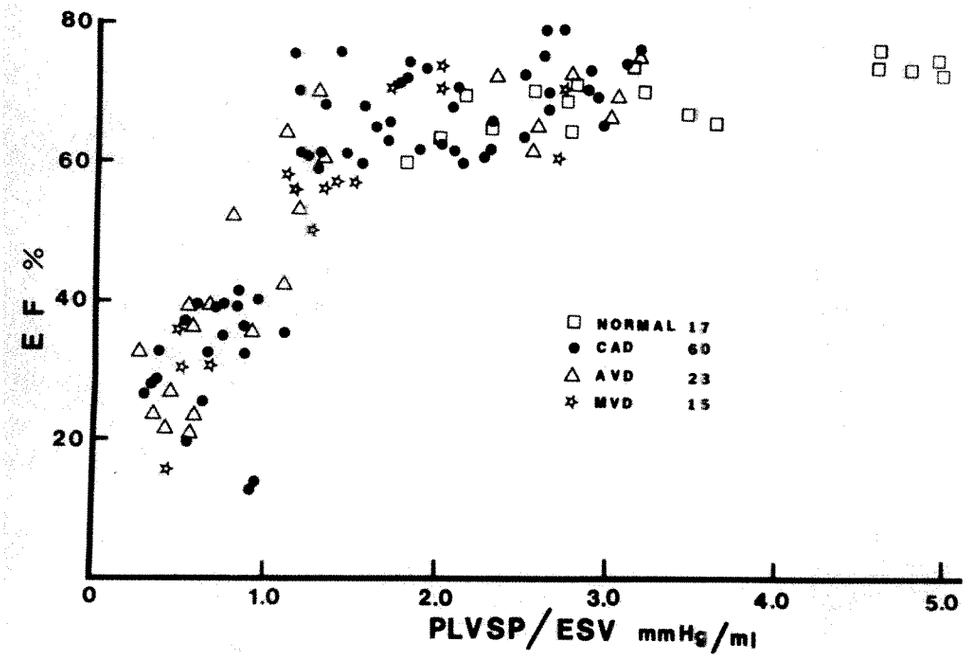


FIGURE 4. Relation of ejection fraction (E F) and peak left ventricular systolic pressure/end-systolic volume (PLVSP/ESV) ratio in patients with a normal heart, coronary artery disease (CAD), aortic valve disease (AVD) and mitral valve disease (MVD).

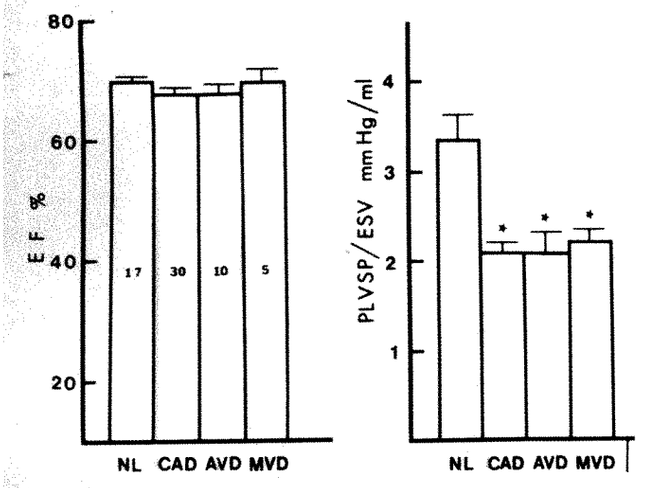


FIGURE 5. Ejection fraction (E F) and peak left ventricular systolic pressure/end-systolic volume (PLVSP/ESV) ratio in patients with a normal heart (NL), coronary artery disease (CAD), aortic valve disease (AVD) and mitral valvular disease (MVD). Results are mean ± SE. Numbers in the bars denote number of patients.

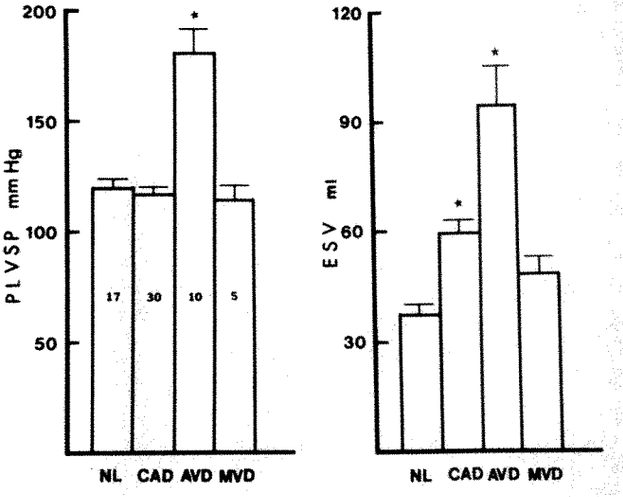


FIGURE 6. Peak left ventricular systolic pressure (PLVSP) and end-systolic volume (ESV) in normal subjects and patients with coronary artery disease (CAD), aortic valve disease (AVD) and mitral valve disease (MVD).

volume (E_{max}), which is thought to be an index of contractility.[4–6,10] Our study shows that the peak systolic pressure just before angiography is not significantly different from the peak systolic pressure during angiography and is similar to the pressure at the time ejection of blood ceases, that is, when the systolic volume is minimal. This finding is similar to those of Rushmer and West in dogs.[8] Also E_{max} and the peak pressure/systolic volume ratio correlate very closely, the latter being 10 percent higher then E_{max}. Therefore, data from a routine catheterization can be used for this measurement.

The assumption that E_{max} can be used as an index of contractility is based on the work of Suga and Sagawa and their co-workers[4,5,10] demonstrating that this index is relatively independent of preload and afterload in the isolated dog heart, yet is sensitive to change in the contractile state. Grossman et al.[6] recently reported that the end-systolic pressure/volume relation is sensitive to inotropic interventions in human hearts. Our findings suggest that it is insensitive to preload and afterload in human subjects. However, further validation of these findings need to be carried out.

One potential drawback of both the peak pressure/systolic volume ratio and the E_{max} measurement in human hearts is that the accuracy of measuring end-systolic volume is uncertain. At this phase of the cardiac cycle, the ventricular geometry deviates most from the ellipsoidal assumption, and the contrast at the blood-wall interface may not be sharp. Nevertheless, this same error is present in other angiographic evaluations of ventricular function such as ejection fraction and analysis of segmental shortening.

Our finding that the relation of E_{max} to ejection fraction in human beings is curvilinear agrees with the theoretical model proposed by Sagawa et al.[10] in which ejection fraction is a complex function of E_{max}, end-systolic pressure and end-diastolic volume. Ejection fraction is preload- and afterload-dependent.[10,11] Thus, it is predictable that ejection fraction would not detect subtle changes in myocardial contractile state and that there might be a high degree of overlap between values in diseased and normal hearts. Because E_{max} and peak pressure/systolic volume ratio are relatively independent of load, they might logically be more sensitive to such subtle changes in contractility.

Clinical implications: The depressed peak pressure/systolic volume ratio in diseased hearts with a normal ejection fraction was found to be largely due to increased end-systolic volume. Grossman et al.[6] also noted that diseased hearts tended to have a larger end-systolic volume. Patients with pure aortic stenosis also might have higher values for peak pressure/systolic volume ratio than normal subjects, but we did not evaluate that condition in our study. Because patients with coronary disease and abnormal wall motion (asynergy or dyskinesia) were excluded from our study, the application of the peak pressure/systolic volume ratio to this group of patients remains to be investigated.

Our study demonstrates increased sensitivity for the peak pressure/systolic volume ratio in detecting heart disease in patients other than those with pure aortic stenosis. The significance of this abnormality relative to the prognostic power of ejection fraction is not known. Also, whether sequential changes in peak pressure/systolic volume ratio will be useful in monitoring the course of patients with heart disease remains to be evaluated.

Acknowledgment

We acknowledge the secretarial skills of Robin Orlansky.

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Monitoring Ventricular Function at Rest and During Exercise With a Nonimaging Nuclear Detector

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A portable nonimaging device, the nuclear stethoscope, for measuring beat to beat ventricular time-activity curves in normal people and patients with heart disease, both at rest and during exercise, is being developed and evaluated. The latest device has several operating modes that facilitate left ventricular and background localization, measurement of transit times and automatic calculation and display of left ventricular ejection fraction. The correlation coefficient of left ventricular ejection fraction obtained with the device and with a camera-computer system was 0.92 in 35 subjects. During bicycle exercise the ejection fraction in 15 normal persons increased from 44 to 64 percent ($P < 0.001$), whereas among 12 patients with heart disease it was unchanged in 5 and decreased in 7.

In 1948 Prinzmetal et al.[1] monitored the passage of an intravenous bolus injection of sodium-24 by means of a Geiger-Muller tube positioned over the heart. Peaks corresponding to right and left ventricular transit were observed. In 1962 Folse and Braunwald[2] conceived of using the electrocardiogram to evaluate end-systolic ventricular volumes and introduced the concept of ejection fraction. Within 6 years, Mullins et al.[3] had developed a device for relating scintillation camera images to the patient's cardiac cycle as measured with the electrocardiogram. Such studies are now widely performed. Typically, the tracer dose of technetium-99m–labeled albumin or red blood cells is allowed to equilibrate in the vascular compartment and the scintillation camera is activated during sequential 10 to 50 msec periods throughout the cardiac cycle. In addition to visualization of the movement of the ventricular walls, a left ventricular time-activity curve is produced. A number of indicators of ventricular performance are derived—ejection fraction, systolic and diastolic time intervals, ejection and filling velocities and ventricular volumes.

Two general types of radiation detectors have been used to produce the left ventricular time-activity curve: imaging devices, such as Anger scintillation cameras, and small "probe" devices that develop the ventricular time-activity curve without visualizing the cardiac structures themselves. In 1976 we[4] described a prototype device of the latter type, which we called a "nuclear stethoscope™." By positioning the detector properly a left ventricular time-activity curve can be generated and beat to beat activity monitored, or multiple beats can be examined to generate a representative ventricular time-activity curve. The device (nuclear stethoscope cardiac probe*) consists of a 2 inch (5.08 cm) thallium-activated sodium iodide crystal with an integrated microcomputer that automatically measures, calculates and displays ejection fraction and several other time and activity measurements during the cardiac cycle on a beat to beat or integrated basis. A high temporal resolution (10 msec) image of the left ventricular time-activity curve is displayed from

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which the operator may select, through the use of cursors, the time and volume positions used in the microcomputer calculation of all left ventricular function indexes.

To allow optimal location of the probe for left ventricular and background counting, the nuclear stethoscope utilizes a unique position/monitoring mode in which changes in beat to beat heart activity can be monitored after equilibration of the tracer. Beat to beat heart activity changes are displayed together with a real time, microcomputer-calculated left ventricular background. This mode is also used in the determination of beat to beat ejection fraction and for intervention studies. The present report describes our results to date with an improved version of the device.

Methods

Operational Design of the Nuclear Stethoscope

Position/monitor mode ("search" mode): This mode is used to locate the optimal probe position for the reproducible measurement of left ventricular and background counts, and for the continuous measurement, calculation and display of beat to beat ejection fraction. The microcomputer calculates and displays the changes in count rate at 50 msec intervals over the heart or the periventricular background region of interest (Fig. 1). These displays facilitate reproducible and optimal localization of the heart and background counting position. After the proper background position has been located and background counts have been stored, the individual heartbeat ejection fraction is calculated by the microcomputer and displayed. The average ejection fraction can also be determined by manually adjusting a cursor to average the peaks and nadirs of the displayed beats. This is done after the cathode ray tube sweep is halted.

Ventricular function mode: After background activity counts have been stored, the probe is repositioned over the heart using the "search" mode and the system is operated in the ventricular function mode. The device automatically acquires scintillation probe counts, gated by the electrocardiographic signal, and organizes the data into a composite left ventricular time-activity curve for two sequential heartbeats (Fig. 2). The internal microcomputer calculates and displays several ventricular function variables according to the position of three operator-adjusted time cursors: T1, T2 and T3. In addition to ejection fraction it is possible to obtain the rate of count change during left ventricular emptying and filling, total count change (a stroke volume), average heart rate during the counting interval, and systolic and diastolic time intervals.

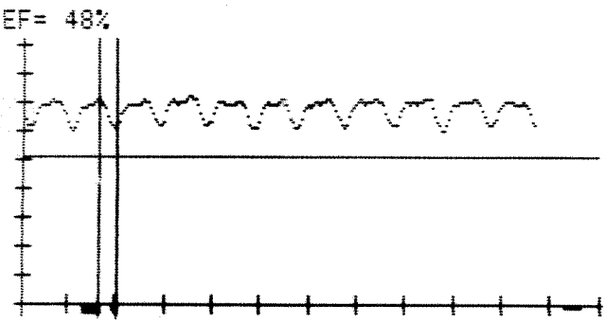


FIGURE 1. The beat to beat time-activity curve during the positioning or monitoring mode. The **horizontal line** is the average background activity. EF = ejection fraction.

First transit mode: In this mode the activity of the right and left ventricles is displayed for a 25 second period during the first transit equilibration of a bolus injection of a radiopharmaceutical agent (Fig. 3). From the stored display of this activity, the operator may select for calculation and display time intervals between any events of interest, such as pulmonary transit time. Also, in this mode, the microcomputer automatically calculates and displays the "cardiac output ratio" C (equil)/C (t)dt, where C (equil) = counts at equilibrium and C (t)dt = integral of counts over time during first transit of the tracer. This ratio when multiplied by patient plasma volume, gives cardiac output. The reliability of these measurements is currently under study. They are based on the use of the Stewart-Hamilton principle.

Clinical Studies

Patients: Using an initial model of the nuclear stethoscope, 48 measurements were made in 30 patients (25 men and 5 women with a mean age [± standard deviation] 46 ± 20 years). Seventy percent had coronary artery disease and 30 percent had other heart diseases. Six normal volunteers were also studied. Interobserver variability in the calculation of left ventricular ejection fraction and background activity was measured by three physician observers. In a subsequent study with the current model of the nuclear stethoscope, 35 patients (24 men and 11 women with a mean age of 54 ± 13 years) were studied at rest by one observer. The effect of exercise was examined in 12 patients (mean age 25 ± 6 years) and in 15 additional normal volunteers.

Procedure: All patients were studied supine after an intravenous injection of 25 mCi of technetium-99m human albumin. The probe of the nuclear stethoscope was first positioned over the left ventricular area, with a 20° to 40° left anterior oblique and a 10° to 20° caudad angulation. The probe was set first in the "search" mode. The position giving the best combination of end-diastolic count rate *and* the greatest stroke volume was taken as the correct left ventricular position. After this position was determined the orientation of the probe was fixed. To determine the background area, the detector was moved laterally in the same plane parallel to the patient's bed until a point of 0 ejection fraction was first reached. Back and forth movement assured that the background taken was the point of nonperiodicity closest to the left ventricle. A reading of background activity was taken over the left ventricle and a time-activity curve was recorded for 60 seconds.

Camera studies were performed with an Ohio Nuclear Model 100 scintillation camera interfaced with an Informatek Simis II computer. An electrocardiographic gate was used to monitor the R waves of each patient's electrocardiogram. Camera images synchronized with the electrocardiogram were obtained for 64 intervals during a cardiac cycle, with the patient lying in a 40° to 50° left anterior oblique position. Eight million counts were obtained in approximately 15 minutes. The left ventricular area of interest was manually selected from a color-coded image in which systole was shown in green and diastole in red.[5] Care was taken to avoid the right ventricle, left atrium and pulmonary vasculature. To obtain the background (extraventricular) activity an area of interest was selected immediately lateral to the left ventricle, but not overlapping the pulmonary artery or the left ventricle, and the background area was generated by computer. The average background was subtracted from the left ventricular curve.

The ejection fraction was then calculated as a ratio of (end-diastolic counts − end-systolic counts)/end-diastolic

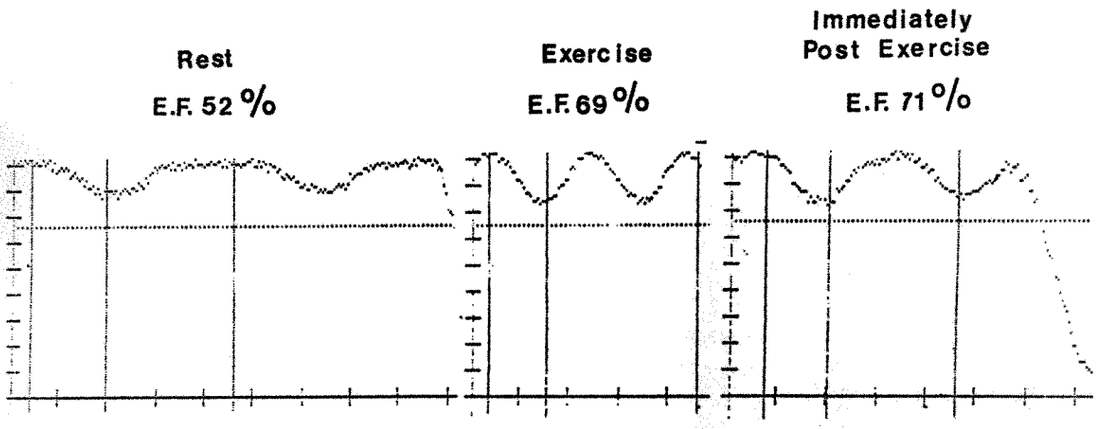


FIGURE 2. Two composite cardiac cycles before, during and after exercise. The disappearance of the diastolic plateau (diastasis) during exercise and its early reappearance after exercise can be seen, as well as the increase in ejection rate and ejection fraction (E.F.).

counts after appropriate background subtraction. Because the nuclear stethoscope has a fixed field of view, we used an end-diastolic region to determine end-diastolic and end-systolic counts on the camera computer system. This gives ejection fractions that are 15 to 20 percent lower than those obtained with contrast angiography.

Exercise studies were carried out on a specially constructed table using a supine bicycle attached to a Warren Collins pedal ergometer. For the nuclear stethoscope studies, the probe was first positioned over the precordium at rest, then background and left ventricular time-activity curves were obtained and left ventricular ejection fraction was calculated. After an initial warm-up period (1 minute at 25 watts), the work load was increased to 50 to 75 watts until the heart rate was stabilized (a further 1 to 2 minutes). The position of the probe was checked by observation of the beat to beat mode and altered if necessary to maximize the difference between end-diastolic and end-systolic counts. A volume-time curve was then recorded in the ventricular function mode and the left ventricular ejection fraction was calculated using the preexercise background. To quantitate the effect of exercise on background activity, a new background measurement was made in nine subjects during or after the stress.

Results

Interobserver variability with the nuclear stethoscope: Interobserver variability was studied in paired measurements of ejection fraction (EF) in 20 patients. For each pair the departure of each individual measurement from the mean of both measurements was expressed as a percent of the mean. The mean ΔEF/mean EF ratio was 10.88 ± 6.33 percent (1 standard deviation) with a range of 0.20 to 20. Expressed in absolute terms, ΔEF was 4.2 units.

This variability was analyzed in terms of the three components involved in the calculation of the ejection fraction (end-diastolic volume, stroke volume and background). The mean percent difference in mea-

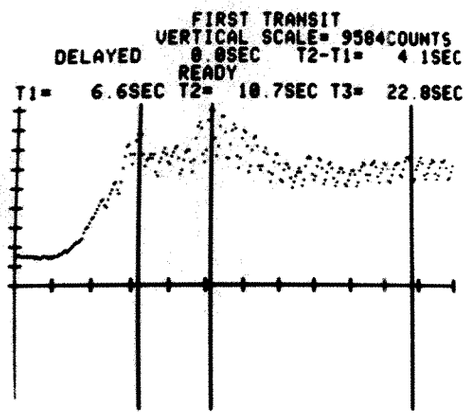


FIGURE 3. The first transit of a bolus injection of technetium-99m human serum albumin through the heart as monitored with the nuclear stethoscope. The initial peak of activity in the right ventricle is followed by the left ventricular peak. The beat to beat changes in activity can be seen. T1, T2, T3 = operator-adjusted time cursors.

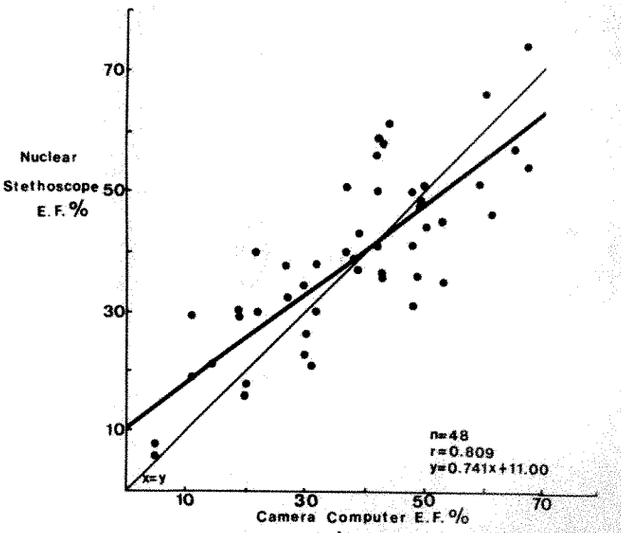


FIGURE 4. Left ventricular ejection fraction (E.F.) in 30 patients (48 observations) examined with an earlier model of the nuclear stethoscope and with a camera-computer system. n = number of observations.

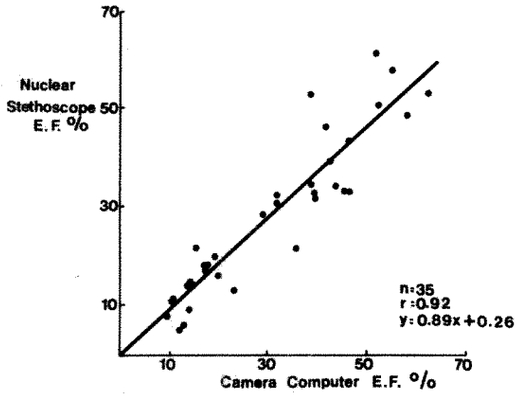


FIGURE 5. A more recent comparison of measurement of left ventricular ejection fraction (E.F.) with the nuclear stethoscope compared with the values obtained with a camera-computer system in 35 patients. n = number of patients.

surement of background was 6.28 ± 4.78 percent (range 0.86 to 21.34). The mean percent difference in measurement of end-diastolic volume was 5.88 ± 13.33 percent (range 0.00 to 44.92).

Comparison of left ventricular ejection fraction by the nuclear stethoscope and camera computer system: Forty-eight observations of left ventricular ejection fraction were made in 30 patients using an early model of the nuclear stethoscope and compared with ejection fraction calculated independently with the camera computer system. The overall correlation was $r = 0.81$, $P < 0.01$ (Fig. 4). With a later model, 35 measurements of left ventricular ejection fraction were made in 35 other patients. The correlation coefficient in these patients was 0.92 ($P < 0.001$) (Fig. 5).

Exercise testing: Figure 6 compares the change in left ventricular ejection fraction with exercise in 15 normal subjects and in 12 patients with heart disease. There was a significant increase in mean ejection fraction from 44 to 64 percent in the 15 normal subjects ($P < 0.001$), whereas in the 12 patients it did not increase (5 patients) or it decreased (7 patients). The mean peak exercise heart rates in the two groups were not significantly different. In six normal subjects who had both nuclear stethoscope and camera-computer studies the ejection fraction showed similar increases during exercise. In four patients with heart disease, both the camera-computer system and nuclear stethoscope showed that ejection fraction was unchanged or decreased during exercise.

Changes in background activity associated with exercise were studied with the nuclear stethoscope, and background values were compared for nine rest/stress pairs, eight stress/post-stress pairs and eight rest/post-stress pairs. The paired t test values were 1.35, 0.458 and −0.7, respectively ($P > 0.05$). Thus, in this series background activity did not change significantly with exercise.

Discussion

The importance of left ventricular ejection fraction in assessing the extent of functional impairment and the

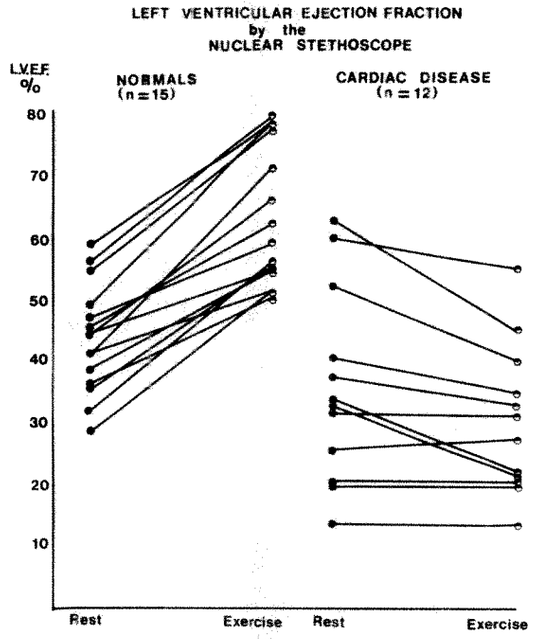


FIGURE 6. During exercise the left ventricular ejection fraction (L.V.E.F.) increased from 44 ± 9 percent to 64 ± 11 percent in 15 normal subjects. In 12 patients with heart disease the ejection fraction decreased or remained the same after exercise. n = number of patients.

prognosis of patients with coronary artery disease is well established.[6-9] Its measurement by means of the scintillation camera and computer is becoming widespread. Our approach is based on the assumption that the usefulness of the camera-computer systems may be extended by a simple portable device that generates the ventricular function curve on a beat to beat or integrated multibeat basis. Such a device may be particularly useful for monitoring changes in global left ventricular function during exercise or other interventions such as drug therapy. With such a device it may be possible to monitor left ventricular function for periods of several hours or longer at the patient's bedside by using technetium-99m–labeled red blood cells.

Current improvements in the nuclear stethoscope: The improved performance of the current device compared with that of prototype models occurs largely because one can properly position the detector while viewing the beat to beat time-activity curve that measures and displays the activity every 50 msec. The position best suited for isolation of the left ventricle from the right ventricle and left atrium is the modified 40° left anterior oblique (15° caudad tilt). The major criteria used to position the detector is to maximize stroke volume and end-diastolic volume as visualized in real time on the display screen. Our results suggest that it is possible to obtain reproducible cardiac localization without the use of radiography or echocardiography. Because technetium-99m–labeled albumin is distributed in structures surrounding the left ventricular chamber, such as the myocardium and lung, a background correction is made by positioning the detector

at the position nearest the ventricle where the time-activity curve first becomes asynchronous.

In earlier studies we examined various collimator designs. Although a multihole parallel hole collimator was best from the standpoint of ease of positioning, its sensitivity was too low. The current version of the nuclear stethoscope uses a converging single hole collimator focused at a point 2 inches (5.08 cm) in front of the collimator face. This provides a field of view large enough to include the left ventricle but with a penumbra small enough to decrease the activity coming from adjacent structures. The converging collimator also makes possible the use of a 2 inch diameter crystal rather than a 4 inch (8.16 cm) diameter crystal that was needed with a parallel hole collimator. This reduces the weight of the probe. The increased sensitivity of the converging collimator allows beat to beat data to be collected and displayed immediately.

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Method for the Rapid and Atraumatic Insertion of Permanent Endocardial Pacemaker Electrodes Through the Subclavian Vein

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Newark, New Jersey

One hundred sixty-four permanent pacemaker implantations through the subclavian vein were accomplished by 17 different physicians at four institutions utilizing a specially constructed peel-away introducer. Fourteen attempts (8.3 percent) to cannulate the subclavian vein were unsuccessful. There were four cases of pneumothorax (2.4 percent) and two cases of hematoma formation (1.2 percent). The procedure has the advantage of a rapid and atraumatic insertion of a variety of transvenous pacemaker electrodes, and the avoidance of surgical dissection for a venous entrance site.

Ninety percent of permanent pacemaker insertions are accomplished utilizing endocardial transvenous electrodes.[1] A cephalic vein is generally used as an electrode introduction site, but frequently the vessel is small and difficult to find. This in turn can lead to extensive dissection and occasionally necessitates exposing the internal jugular or subclavian vein.

An introducer sheath has been used for permanent transvenous electrode implantation in the past. Two methods have been described: Batson[2] and Jahuck et al.[3] used a disposable catheter introducer when inserting electrode wires that had no hub or connector, thus allowing the introduction sheath to be removed from the distal end of the electrode. Other groups[4–8] used the no. 9 Desilets-Hoffman sheath minus its metal hub, which was used as an introducer for a small unipolar electrode. The sheath was then removed from the electrode by cutting it away longitudinally with a pointed scalpel.

In this report we describe the utilization of a specially constructed "presplit," semirigid radiopaque polyethylene sheath that can be used to introduce a wide variety of transvenous electrodes through the subclavian vein.

Method

Device: The device consists of four essential parts (Fig. 1F): (1) a 9 cm, 18 gauge thin wall needle; (2) a 50 cm, 0.036 spring guide wire with "J" tip; (3) a 23 cm, no. 8F Teflon® vessel dilator; and (4) a 16 cm, tapered radiopaque, semirigid polyethylene sheath that tapers from 13F to 11F with an 8F terminal narrowing, the sheath being longitudinally split to within 2 mm of its terminus (a larger sheath is required for bipolar electrodes).*

Procedures: The upper chest is surgically prepared. After infiltration of a local anesthetic agent into the proximal intraclavicular area, the no. 18 gauge thin wall needle is inserted just medial to the junction of the middle and inner thirds of the clavicle, aiming the needle slightly above and behind the suprasternal notch (Fig. 1A). If difficulty is encountered in puncturing the subclavian vein, the patient's legs are raised or the table is put in Trendelenburg's position to increase the venous pressure and to distend the vein. When the vein has been punctured, a 50 cm spring guide wire with a "J" tip is inserted into the subclavian vein through the needle and then into the superior vena cava under fluoroscopic

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* The device is available in multiple sizes (unipolar, bipolar and atrial-J) from Cordis Corporation, Miami, Florida and the Daig Corporation, Minnetonka, Minnesota).

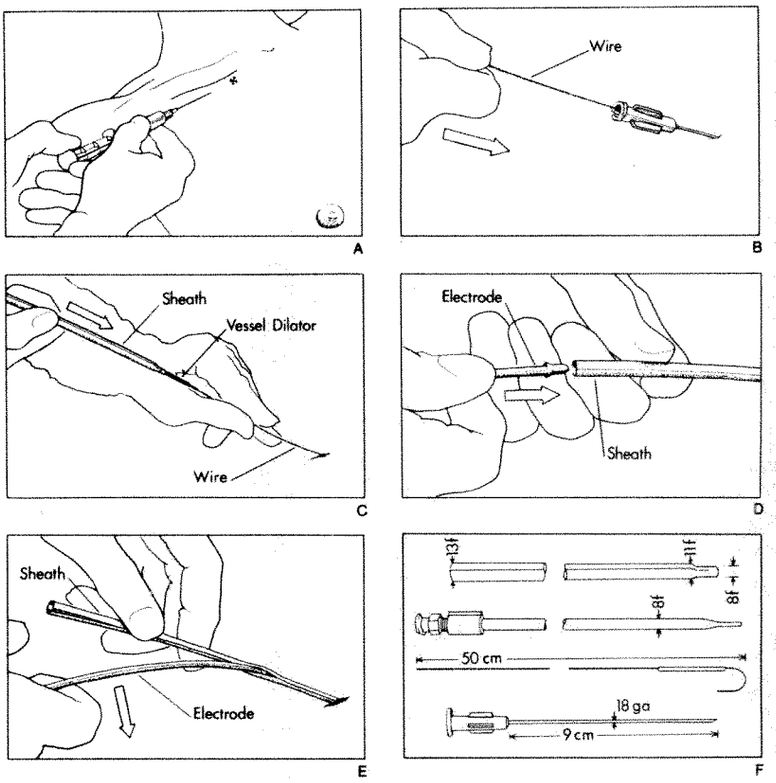


FIGURE 1. A, insertion of subclavian vein needle. **B,** insertion of the "J" wire. **C,** insertion of the sheath and vessel dilator into the subclavian vein; **D,** insertion of the electrode into the sheath; **E,** peeling off of the sheath from the electrode; **F,** components of the introducer kit.

control, leaving 15 to 20 cm of the wire exposed (Fig. 1B). At that time, the incision is extended to 7 to 8 cm laterally from the puncture site, and a subcutaneous pocket is made for the pulse generator. While the pocket is allowed to "dry," the vessel dilator and tapered split sheath are inserted over the wire as one unit (Fig. 1C) and with moderate force pushed through the subclavian fascia into the subclavian vein leaving 3 to 4 cm of the sheath and vessel dilator exposed. (One of us (V.P.) prefers to make the incisions and prepare the pocket first, then inserting the needle through the opened wound.)

The wire and vessel dilator are then removed, leaving the split sheath as a conduit into the subclavian vein and superior vena cava. A unipolar electrode, which has been prelubricated with a light coat of sterile lubricant is inserted into the superior vena cava through the sheath (Fig. 1D) and into the subclavian vein and superior vena cava. (Originally we used sterile mineral oil as a lubricant, but it is probably preferable to use hypertonic glucose, Renografin 76® or sterile water-soluble surgical jelly.) With the electrode in the right atrium, the sheath is then pulled back and peeled off from the electrode by separating it along the longitudinal split (Fig. 1E), care being taken not to pull out the electrode while the peeling operation is taking place.

The electrode is then manipulated in the usual manner, and when a satisfactory position in the heart has been obtained the lead is fixed to the underlying fascia, putting the ligatures or Silastic clamp as close as possible to the entrance site of the subclavian fascia. We used permanent unipolar electrodes of various types (Arco, Biotroniks, Cordis, Coratomic, CPI, Edwards, Intermedics, Medtronics, Teletronics, Vitatron). The pulse generator is then connected to the wire and inserted in the subcutaneous pocket. A chest X-ray film is taken within 1 hour of the procedure to exclude the presence of pneumothorax.

Results

Between November 1, 1977 and August 30, 1978, a total of 164 electrodes were implanted by 17 physicians at four institutions: Florida Hospital, Orlando, Florida; Miami Heart Institute, Miami, Florida; Newark Beth Israel Medical Center, Newark, New Jersey; and St. Thomas Hospital, Nashville, Tennessee. In 14 cases (8.5 percent) this method was unsuccessful; the electrode was then inserted in the usual manner through the cephalic vein.

The patients were carefully observed in the postoperative period for pneumothorax, hematoma formation, mediastinal widening, wound infection, general patient discomfort and lead displacement. (We do not believe lead stability is related to the method of lead insertion. There were three instances of lead displacement in 150 patients, a lesser incidence than is generally seen in most patient groups with a pacemaker.[1]) There were four cases of pneumothorax, two requiring insertion of chest tubes. The patients recovered uneventfully. All four cases occurred in the first half of the series. Two wound hematomas occurred. Both patients were receiving anticoagulant agents. One patient complained of pain in the arm at the time of insertion and in the immediate postoperative period, presumably because of a brachial plexus trauma. These symptoms disappeared within 1 week.

The time elapsed from the initial needle puncture to the time of electrode insertion into the right atrium ranged from 90 seconds to 15 minutes, with a median time of 4 minutes.

Discussion

Advantages of technique: Several features of the device should be noted. The no. 18 gauge thin wall needle has a far smaller cross-sectional area than the traditionally used no. 14 gauge needle, thus lessening the danger of a repeated arterial, venous or pleural puncture. The tapered, semirigid sheath with its terminal narrowing allows easy penetration of the subclavian fascia without the "accordian effect" seen with many catheter introducer sheaths, and without tearing of the venous wall. The split in the sheath, which is essential for its removal from the catheter, allows the sheath to expand to accommodate a variety of catheter types and sizes (phlanged, small tines, corkscrew, and so forth).

The principal advantages of the technique are the rapidity with which a catheter can be introduced into the right atrium and the limited dissection required to accomplish the implantation. This leads to an atraumatic procedure with less risk of wound infection and less patient discomfort. An added advantage is the ease with which the catheter can be manipulated through the fascial and venous puncture. An important potential advantage is the future use of multiple electrode systems such as the atrioventricular sequential pacemakers.

Complications: The ease and rapidity of the procedure tend to be directly proportional to the physician's familiarity with subclavian puncture. Most of the aforementioned complications occurred during the implanting physician's initial use of the technique. Our greatest concern was the possibility of pneumothorax. This turned out to be an infrequent problem (total of four cases [2.4 percent]). Although two patients required chest tubes, there were no permanent sequelae. All 4 cases occurred in the first 76 cases of the series.

Leakage around the venous puncture site with hematoma formation was our second concern. This did not materialize. The two patients who had hematomas were already receiving anticoagulant agents preoperatively. There was no evidence of perielectrode venous leakage, and its lack probably relates to the snug fit of the venous adventitia around the electrode catheter.

Accidental subclavian arterial punctures by the needle were observed in six cases, but no evidence of bleeding, subclavian hematoma or mediastinal widening was noted (this is probably related to the small caliber of the puncturing needle). The one patient presumed to have brachial plexus trauma had no sequelae. No cases of hemothorax, air embolism, wound or guide wire infection were noted.

In 14 patients the technique was abandoned because of inability of the physician to cannulate the subclavian vein. Eight of 14 failures were reported by 2 of the 17 physicians.

Recommended guidelines for avoiding complications and failures: Obviously, the technique used by the physician in the subclavian venous needle puncture is the key to a simple and complication-free procedure. It helps to observe the following guidelines:

1. When there is no concern about congestive heart failure, it would be advisable to keep the patient relatively well hydrated before the procedure to avoid a low central venous pressure and a "flat" subclavian vein.
2. Trendelenburg's position is a great aid in distending the subclavian vein. If this is not possible, use of a large foam wedge for elevation of the legs is helpful.
3. It is wise to approach the subclavian vein as medially as possible, still allowing enough room for easy passage of the device between the clavicle and first rib, thus minimizing the possibility of pleural puncture.
4. It is well to avoid excessive repeated needle punctures.
5. If "air is struck," the patient should be carefully observed and, if his condition is stable, the standard cephalic vein technique should be used or the opposite side approached. (Pneumothorax can sometimes be detected fluoroscopically.)

Implications: This method of inserting a permanent pacing electrode is rapid and atraumatic and useful for the introduction of a wide variety of permanent transvenous pacemaker electrodes. If the approach to the subclavian puncture is undertaken carefully, the procedure has minimal risk. Because of the ease of its use and the reduction of the occasionally tedious dissection of difficult veins, it has been enthusiastically received by both the implanting physicians and operating room personnel. It has the potential for facilitating multiple electrode insertions such as those being used with the new double electrode, double chamber systems.

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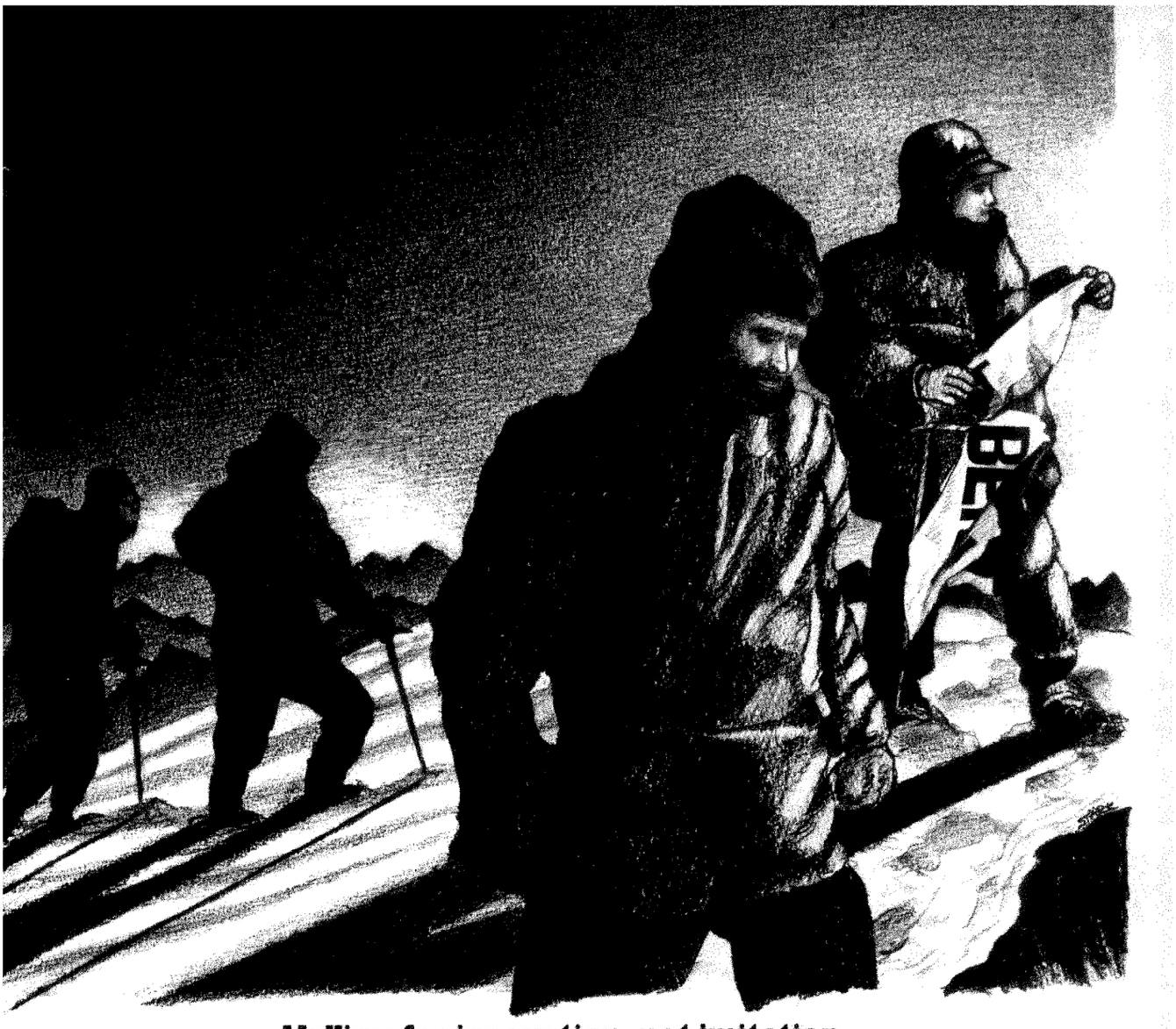
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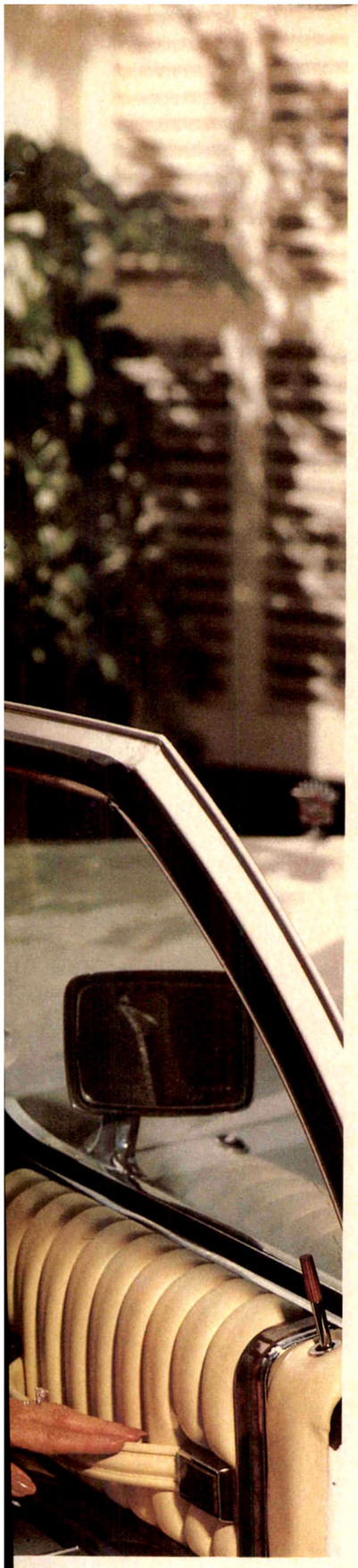
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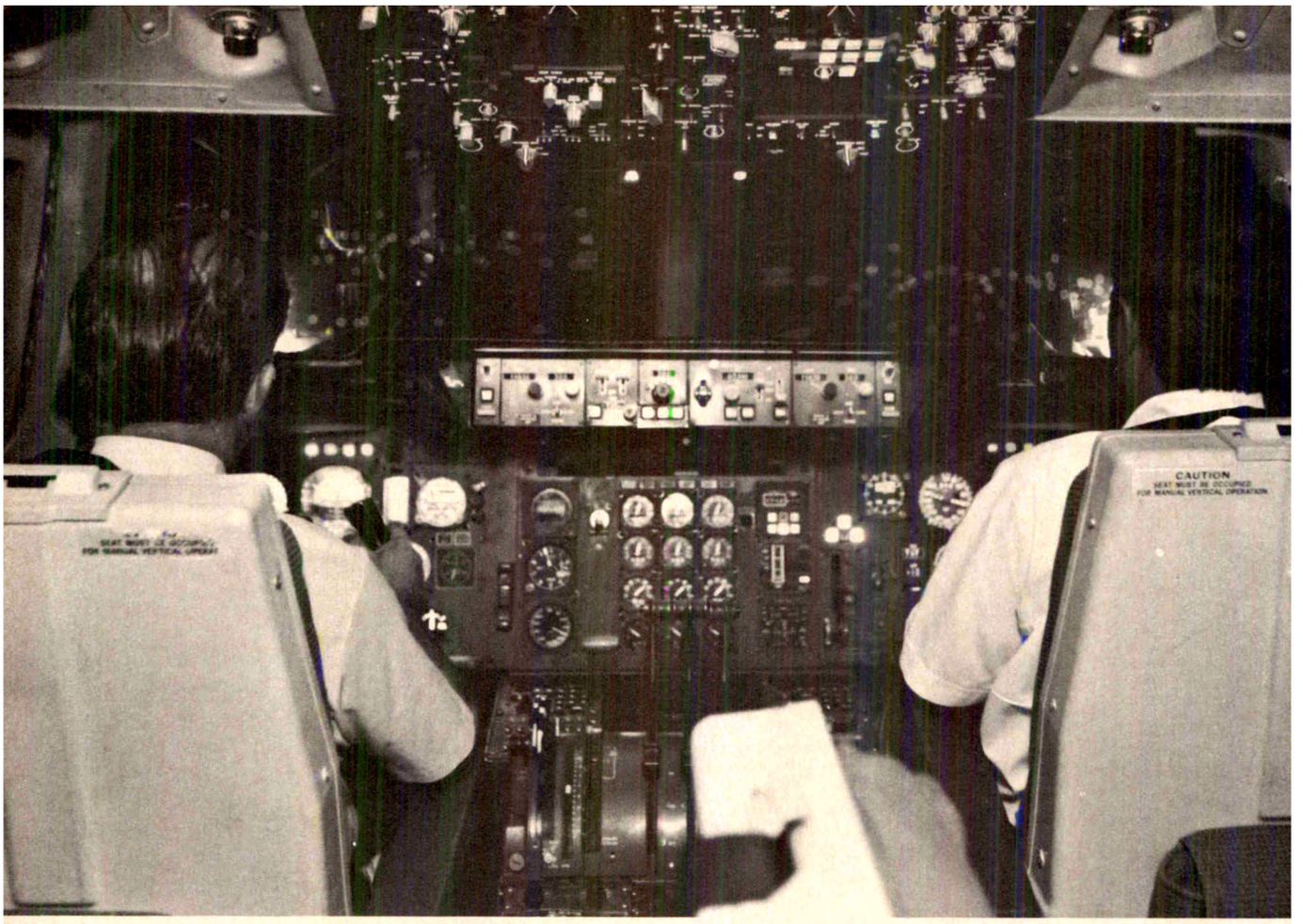
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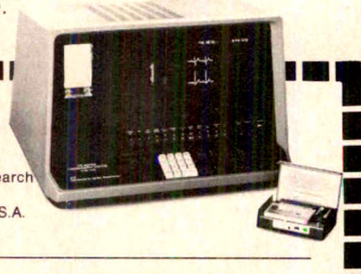
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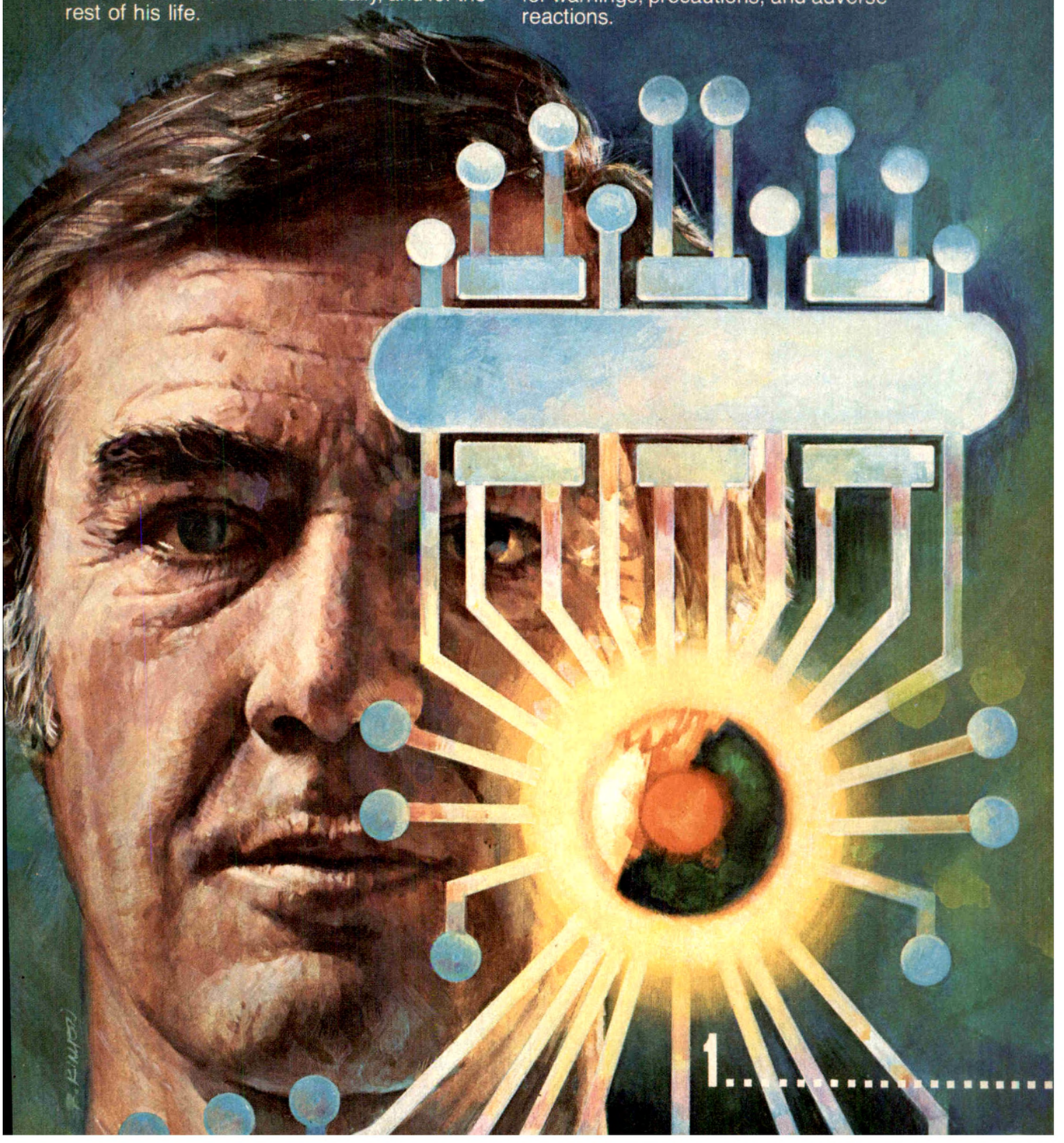
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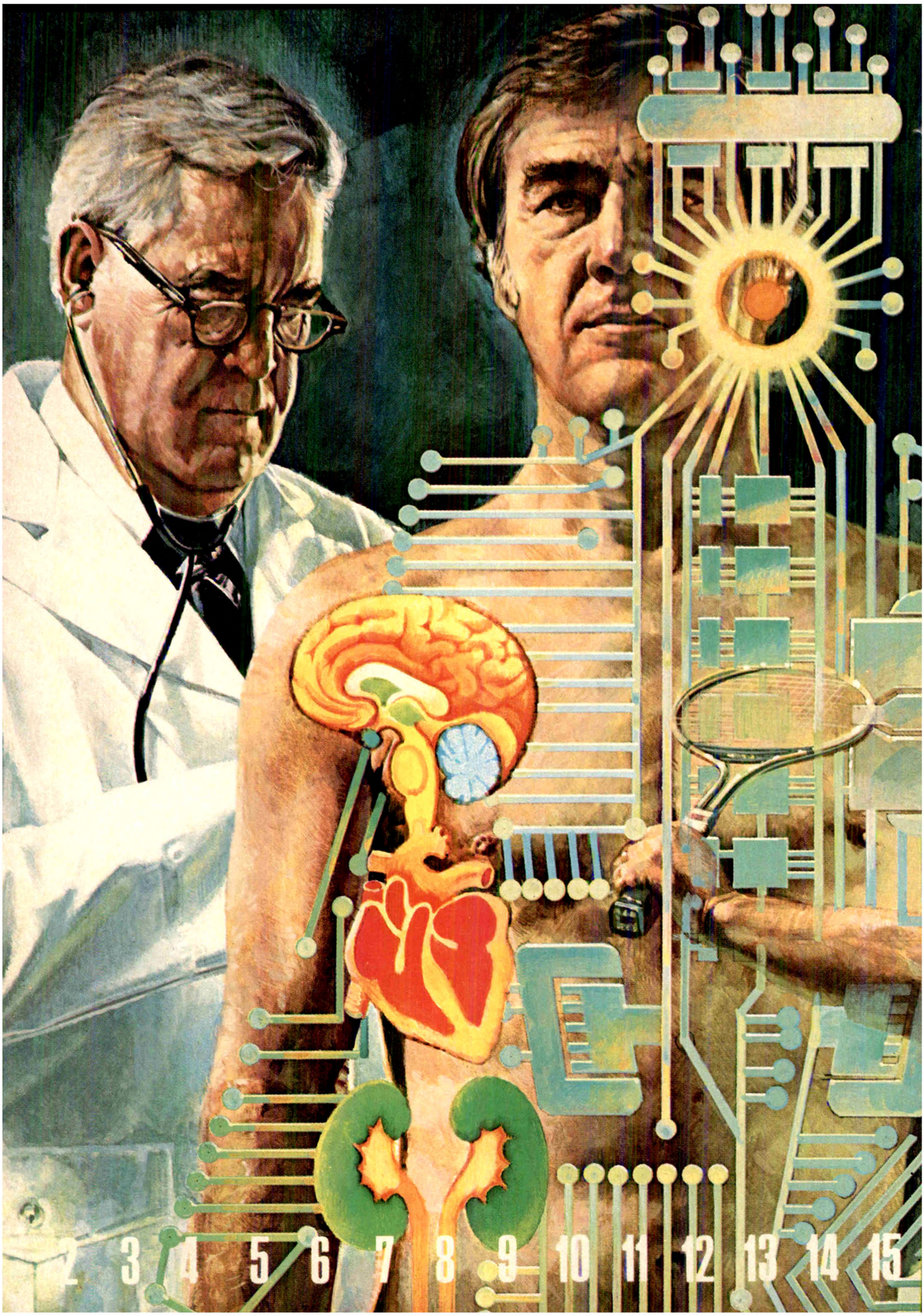
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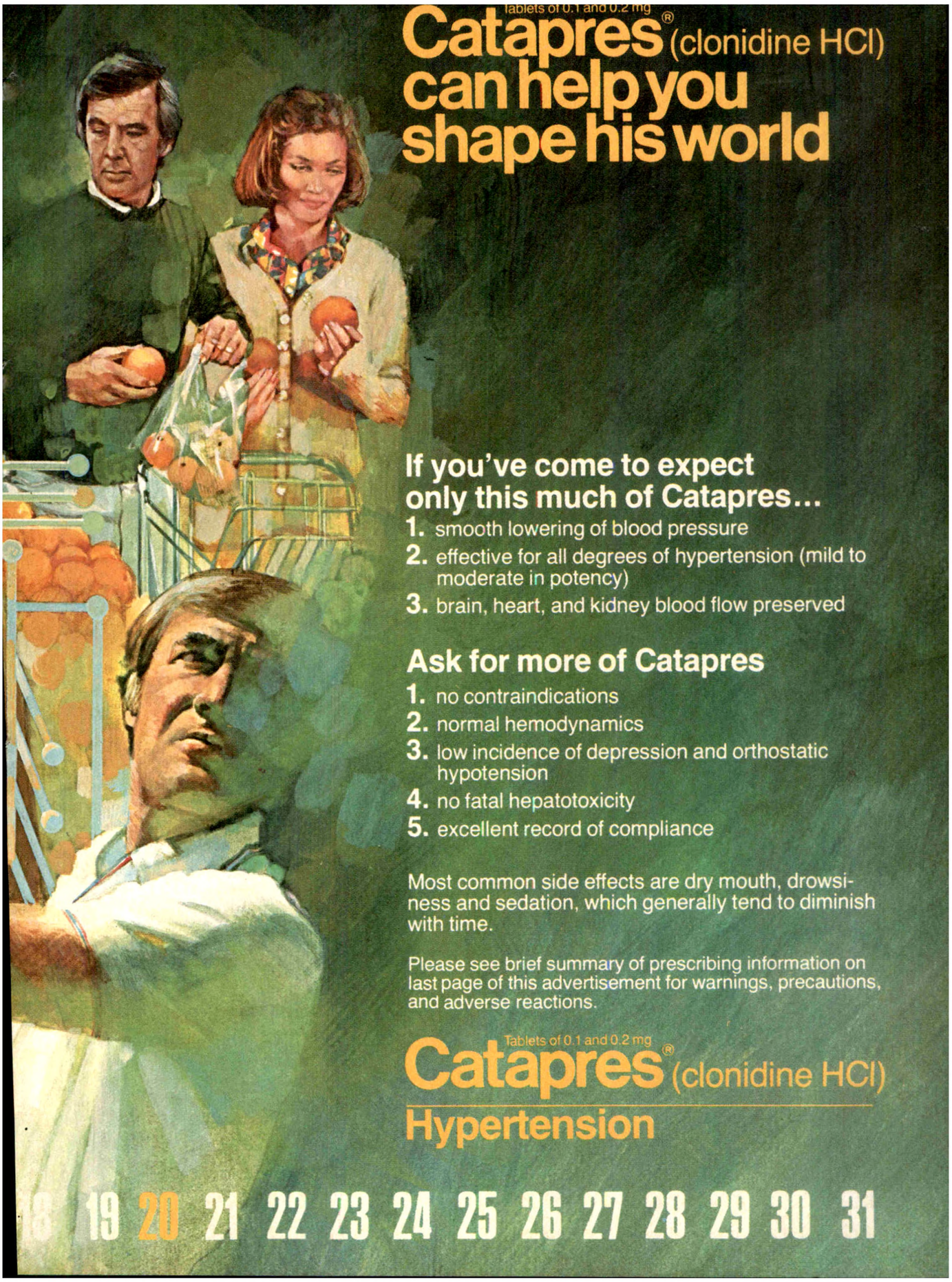
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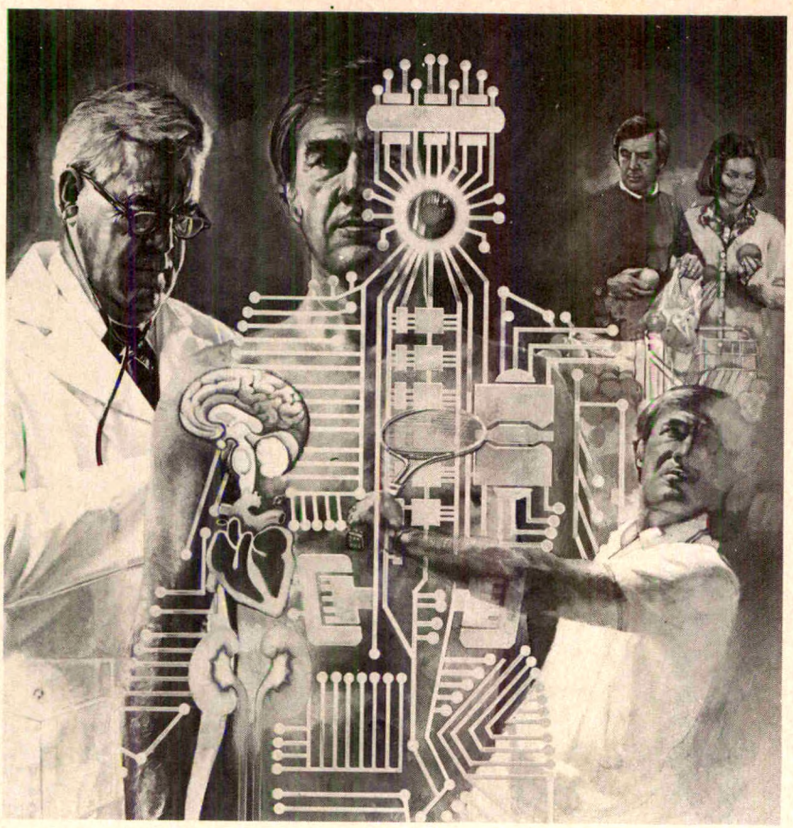
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Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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Effects of Digoxin on Sinus Nodal Function Before and After Vagal Blockade in Patients With Sinus Nodal Dysfunction

A Clue to the Mechanisms of the Action of Digitalis on the Sinus Node

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To increase the limited knowledge of the effects of digitalis on sinus nodal function in patients with sinus nodal dysfunction and to initiate an investigation into the mechanisms underlying its effects, 34 patients with sinus nodal dysfunction were studied. Twenty patients underwent determination of sinus cycle length, estimated sinoatrial conduction time and maximal corrected sinus recovery time before and after the administration of 0.75 mg of intravenous digoxin. For the group, sinus cycle length did not change, sinoatrial conduction time increased insignificantly and maximal corrected sinus recovery time shortened; however, individual variation occurred. The effects of acute digitalization appeared to predict the effects of chronic digitalis administration on sinus nodal function in the eight patients who subsequently continued to take digoxin. Fourteen patients received digoxin after vagal blockade with atropine. After vagal blockade, digoxin lengthened sinus cycle length, sinoatrial conduction time and maximal corrected sinus recovery time. The effects of digoxin administered after atropine could be antiadrenergic, direct, or both, and are opposite to those induced by atropine alone. Because these effects are similar to those of vagotonia yet are not apparent when the vagi are unblocked, digoxin may have direct excitatory, adrenergic or previously unrecognized vagolytic effects on sinus nodal function in man and their manifestation may be dependent on heart rate or autonomic tone.

The safety of digitalis therapy in the presence of sinus nodal dysfunction is a common and controversial issue. Both the presence[1-6] and absence[2,7-12] of exacerbated sinus bradycardia, sinoatrial arrest and sinoatrial exit block after digitalis have been reported. Recently, ambulatory monitoring,[11,12] maximal treadmill tests[11] and atrial stimulation[7,11-17] have been utilized to define more clearly the effects of digitalis on the sinus node both in patients with normal[13-15] and abnormal[7,11,12,16] sinus nodal function and in patients who have had cardiac transplantation[17] (Table I). Most of these studies found insignificant changes in resting and exercise sinus rates, slight prolongation of sinoatrial conduction time and shortening of postoverdrive sinoatrial recovery time by digoxin or ouabain. However, the results of these studies are not completely uniform, the total number of patients studied is still small and none of these studies attempted to evaluate the mechanism by which digoxin affects sinus nodal function in man. Accordingly, our study was undertaken (1) to add to the number of patients with sinus nodal dysfunction in whom the effects of digitalis on sinus nodal function have been evaluated, and (2) to initiate investigation into the pathways by which digoxin's actions on sinus nodal function are mediated.

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TABLE I

Previously Reported Effects on Sinus Nodal Function in Man

Authors	Subjects no.	Subjects Type	Drug	SCL (msec) C	SCL (msec) Dig	Maximal CSRT (msec) C	Maximal CSRT (msec) Dig	SACT (msec) C	SACT (msec) Dig
Engel and Schaal[7]	14	SND	Ouabain, 0.01 mg/kg	1035	1053	1113	693*	. . .	. . .
Bond et al.[14]	5	"Normals"	Ouabain, 0.01 mg/kg	. . .	. . .	. . .	. . .	X	X + 27*
Dhingra et al.[13]	16	"Normals"	Ouabain 0.01 mg/kg	887	905	226	103*	90	110*
Cummings et al.[12]	14	SND	Ouabain 0.015 mg/kg	1091	1017	514	244*	. . .	. . .
Vera et al.[11]	9	SND	Digoxin, 0.04 mg/kg	1053	984	714	565	. . .	. . .
Goodman et al.[17]	5	"Normals"	Digoxin, 1.25 mg	788	828	129	172	107	119
Goodman et al.[17]	6	Cardiac transplant	Digoxin, 1.25 mg	561	561	225	245	73	104*†

* $P < 0.05$.

† Sinoatrial Wenckebach block developed in one patient and 2:1 sinoatrial exit block in another.

C = control; CSRT = corrected sinus recovery time; Dig = digitalis; "normals" = patients undergoing cardiac catheterization for evaluation of symptoms or heart disease without precatheterization evidence of sinus nodal dysfunction; SACT = estimated sinoatrial conduction time; SCL = sinus cycle length; SND = sinus nodal dysfunction; X = control (value not given by authors[14]).

Method

Patients

A total of 34 patients were studied. All had undergone 12 or 24 hours of continuous electrocardiographic recording before enrolling in the study. Eleven had sick sinus syndrome as defined by sinoatrial arrest, sinoatrial exit block, the bradycardia-tachycardia syndrome or marked sinus bradycardia with periods of sinus rates of less than 40 beats/min while the patient was awake.[18] Twenty-three patients had lesser degrees of persistent or intermittent sinus bradycardia as defined by sinus rates of less than 60 beats/min in the awake state. All patients underwent right heart catheterization in the resting, nonsedated postabsorptive state after written, informed consent was obtained. None had received cardioactive medications in the 5 days preceding the study.

Atrial Stimulation Studies

In a manner previously described,[19] two recording-stimulating catheters were positioned in the right atrium, atrial premature stimulation was performed, the peristimulation cycles were analyzed and an estimated mean sinoatrial conduction time was determined. Additionally, atrial overdrive pacing for 30 seconds was performed at cycle lengths of 400, 500, 600, 700, 800, 900, and 1,000 msec and longer if the spontaneous sinus rate permitted. Pacing was begun at the longest cycle length that allowed complete capture of the atrium, and the cycle length was progressively shortened to 400 msec. Thirty seconds of recovery separated the pacing runs. This sequence was repeated four times.

When atrial pacing was performed, the following intervals were measured: (1) the interval from the last driven atrial depolarization to the next spontaneous depolarization of any type, and (2) the interval from the last driven atrial depolarization to the next spontaneous P wave if this was different from the first interval. The sinus recovery time was defined as the interval from the last driven atrial depolarization during atrial pacing to the next spontaneous P wave if it was of sinus origin. The corrected sinus recovery time was defined as the sinus recovery time minus the mean sinus cycle length,[18,20]

TABLE II

Clinical Findings in 20 Patients Given Intravenous Digoxin Without Prior Vagal Blockade

Case no.	Age (yr) & Sex	LVF	HD	HS	SSS
1	65 M	. . .	U	N	−
2	77 M	. . .	CSD	N	+
3	31 M	. . .	N	N	−
4	78 M	+	ASCVD	I	+
5	61 F	. . .	N	N	−
6	23 F	. . .	RHD	N	−
7	67 F	. . .	HCVD	I	−
8	61 F	. . .	HCVD	I	−
9	77 F	. . .	HCVD and AI	N	−
10	76 F	+	HCVD	I	−
11	62 M	. . .	HCVD	N	+
12	75 F	+	ASCVD	I	−
13	69 F	. . .	HCVD	N	−
14	70 F	+	ASCVD	I	−
15	66 M	+	HCVD	I	+
16	74 M	. . .	ASCVD	N	−
17	85 M	. . .	AS	I	+
18	65 M	+	C	I	−
19	56 F	. . .	N	N	−
20	61 F	. . .	ASCVD	N	+

AI = aortic insufficiency; AS = aortic stenosis; ASCVD = arteriosclerotic cardiovascular disease; C = cardiomyopathy; CSD = primary conduction system disease; HCVD = hypertensive cardiovascular disease; HD = heart disease; HS = heart size; I = increased; LVF = left ventricular failure; N = normal; RHD = rheumatic heart disease; SSS = sick sinus syndrome[18] (see Methods); U = heart disease of unknown etiology; + = present; − = absent.

and the maximal corrected sinus recovery time was defined as the longest of all the observed corrected sinus recovery times.

Twenty patients were given 0.75 mg of digoxin intravenously over a period of 10 to 15 minutes immediately after their control studies. Forty-five minutes later atrial stimulation was repeated. Clinical findings in these 20 patients are presented in Table II.

Fourteen additional patients were given atropine intravenously after their control studies (see later). In these 14 patients the atrial stimulation procedures were repeated 5 minutes after the administration of atropine. Digoxin was then given as described, and 45 minutes later the atrial stimulation studies were repeated.

Results

The results are presented in Table III.

Sinus cycle length: In patients receiving digoxin without prior vagal blockade, sinus cycle length increased in 10, decreased in 8 and was unchanged in 2 after digoxin. The group's mean sinus cycle length did not change significantly, being 1,003 msec before and 1,051 msec after digoxin. Only three patients had a change in sinus rate greater than 5 beats/min and only one had a change in sinus rate greater than 10 beats/min (62 to 48 beats/min). None of the clinical findings (Table II) were associated with a particular directional change in sinus cycle length after digoxin.

TABLE III

Effects of Digitalis on Sinus Nodal Function in 20 Patients With and Without Vagal Blockade

Case no.	Before Digoxin* SCL	SACT	CSRT	After Digoxin† SCL	SACT	CSRT
A. Without Vagal Blockade (20 patients)						
1	1110	80	655	1069	117	527
2†	1095	145	1037	1076	128	984
3	973	111	443	1040	86	287
4†	881	. . .	. . .	861	. . .	. . .
5	746	120	339	747	98	223
6	951	97	443	1040	101	330
7	728	. . .	271	695	. . .	275
8	1193	109	479	1280	98	302
9	1077	88	201	1063	75	288
10	801	101	414	807	115	151
11†	1205	187	726	1458	230 + SAW	722
12	1232	82	502	1197	106	292
13	966	106	449	1237	67	169
14	817	114	308	893	104	312
15†	1174	76	2642	1172	90	193
16	1147	131	418	1189	148	333
17†	1007	32	1108	1042	51	370
18	1088	83	399	1116	77	250
19	1192	105	382	1305	112	300
20†	677	. . .	215	735	. . .	181
Mean	1003	104	602	1051	106	342
±S.D.	±176.3	±33.1	±550.7	±207.5	±39.5	±203.6
B. After Partial Vagal Blockade (7 patients)						
1	518	31	52	592	39	248
2	685	63	178	696	85	219
3	640	69	184	704	93	257
4†	657	46	261	734	85	811
5†	861	95	210	974	124	372
6	733	45	217	959	86	361
7	781	70	249	821	82	271
Mean	696	60	193	783	85	363
±SD	±109.8	±21.1	±69.3	±142.3	±24.9	±205.8
C. After Complete Vagal Blockade (7 patients)						
1†	571	116	224	605	150	343
2†	579	74	172	591	74	204
3	682	60	257	835	103	288
4	640	. . .	323	659	. . .	414
5†	560	. . .	195	586	. . .	. . .
6	711	. . .	604	795	. . .	. . .
7	530	45	101	638	68	127
Mean	610	74	268	673	99	361
±SD	±67.9	±30.6	±163.5	±101.2	±37.4	±233.6
B + C. After Partial or Complete Vagal Blockade (14 patients)						
Mean	657	65	233	729	89	362
±SD	±98.8	±24.4	±131.5	±131.7	±29.0	±209.5

* Values in these columns refer, respectively, to control values before digoxin (A), values after administration of 1 mg of atropine (B) and values after administration of atropine until complete vagal blockade occurred (C).

† Patients with electrocardiographically recognized sick sinus syndrome before study.

CSRT = corrected sinus recovery time (msec); SACT = sinoatrial conduction time (msec); SAW = sinoatrial Wenckebach phenomenon; SCL = sinus cycle length (msec); SD = standard deviation.

Sinoatrial conduction time: Prolongation of the post-return cycle (A_3-A_4)[19] prevented estimation of sinoatrial conduction time in three patients who received digoxin without atropine. In the remaining 17 patients, estimated sinoatrial conduction time increased in nine and decreased in eight patients after digoxin. The mean value of 106 msec after digoxin was slightly but not significantly greater than the mean value of 104 msec before digoxin. Sick sinus syndrome was the only clinical characteristic (Table II) associated with a particular directional change in sinoatrial conduction time after digoxin. After digoxin three of the four patients with sick sinus syndrome and sinoatrial conduction time determinations had a lengthened sinoatrial conduction time. Although the prolongation in two of these three patients was less than 40 msec, sinoatrial Wenckebach block developed in one patient, thus demonstrating that digoxin can have clinically detrimental effects on sinoatrial conduction in patients with sick sinus syndrome.

Maximal corrected sinus recovery time: This interval was determined before and after digoxin in 19 patients without prior vagal blockade. Technical difficulties prevented atrial overdrive pacing in one patient. For the group, digoxin shortened the mean value for maximal corrected sinus recovery time from 602 ± 551 msec (mean ± standard deviation) before to 342 ± 204 msec after digoxin ($P < 0.01$). Because the distribution of the differences between maximal corrected sinus recovery time before and after digoxin was strikingly abnormal and had an extremely wide range, the sign rather than the t test was used as the statistical test. The response to digoxin was much less predictable in subjects with long control values for maximal corrected sinus recovery time than in other subjects. This fact is responsible for the abnormal distribution of the differences in the individual patient's maximal corrected sinus recovery times before and after digoxin and their large standard deviations (557 msec).

Individually the maximal corrected sinus recovery time decreased in 15 patients, was unchanged in 3 and increased by only 87 msec in 1 patient after digoxin. In two patients, one of whom had the bradycardia-tachycardia syndrome, the shortening of maximal corrected sinus recovery time exceeded 300 msec. The shortening of this interval after digoxin has beneficial clinical therapeutic implications for patients with the bradycardia-tachycardia syndrome.

Chronic digitalization: Nine of these 20 patients had clinical indications for digitalization and continued to receive digoxin therapy after its initiation during catheterization. They had not been receiving digitalis previously. Eight of the nine have been available for follow-up study for 11 to 55 (mean 39) months. The one patient in whom Wenckebach block developed during electrophysiologic study was given a permanent sinoatrial pacemaker and continues to have sinoatrial block. The seven others had no significant deterioration of sinus nodal function during acute study and have tolerated long-term digitalization without difficulty. One of these seven was restudied a week after his maintenance regimen was begun and had no significant change in sinus nodal function from that in the acute study.

Digoxin after vagal blockade: Seven patients received a single 1 mg bolus injection of atropine before administration of digoxin. After atropine, the mean values for sinus cycle length, sinoatrial conduction time and maximal corrected sinus recovery time for this group were 696, 60 and 193 msec, respectively. After the subsequent administration of digoxin, in all seven patients sinus cycle length increased (mean 783 msec), sinoatrial conduction time increased (mean 85 msec) and maximal corrected sinus recovery time increased (mean 363 msec).

To be certain that 1 mg of atropine offered sufficient vagal blockade before the administration of digoxin to yield meaningful results, seven additional patients received incremental doses of atropine until complete vagal blockade had occurred before digoxin was given. This was achieved by administering atropine at 5 minute intervals in individual doses of 0.1, 0.2, 0.2, 0.2, 0.3 and then 1 mg each until the sinus rate no longer increased. A total of 2 to 4 mg was required in individual patients. After incremental atropine the mean values for sinus cycle length, sinoatrial conduction time and maximal corrected sinus recovery time for this group were 610, 74 and 268 msec, respectively. After the subsequent administration of digoxin the sinus cycle length increased (mean 673 msec) in seven of seven patients, and the maximal corrected sinus recovery time increased in all six patients who underwent atrial overdrive pacing (mean 361 msec). Catheter instability prevented determination of the maximal corrected sinus recovery time in the remaining patient.

Estimation of sinoatrial conduction time was interpretable in only four patients who received digoxin after total vagal blockade because prolongation of the post-return cycle (A_3-A_4) prevented meaningful estimation in two patients and catheter instability prevented it in one. In these four patients, sinoatrial conduction time increased in three and was unchanged in one (mean values 74 msec before and 99 msec after digoxin). When the remarkably similar results in the two groups of patients given atropine are pooled, it can be seen that when digoxin was administered after vagal blockade sinus cycle length lengthened in 14 of 14 patients (223 to 362 msec) ($P < 0.01$), maximal corrected sinus recovery time lengthened in 13 of 13 patients (657 to 729 msec) ($P < 0.01$) and sinoatrial conduction time lengthened in 10 of 11 patients (65 to 89 msec) ($P < 0.01$) but was unchanged in one.

Discussion

Mechanisms of effects of digitalis on mammalian sinoatrial node: Our results and those of previous investigations of human subjects may seem a little unexpected in light of most of the available knowledge of the effects of digitalis on the mammalian sinus node. For example, acute administration of therapeutic doses of digitalis to intact mammals usually causes sinus slowing rather than no change.[21–29] This slowing, which occurs in several species, has been attributed to vagal[21–25,28,29]

or antiadrenergic mechanisms,[22,26,27] or both, but not to direct effects of digitalis on the sinoatrial node. Digitalis promotes vagal activity by hypersensitizing carotid sinus baroreceptors,[21,28,29] stimulating the central vagal nucleus and nodose ganglia,[21] and directly potentiating efferent vagal impulses.[21,23] Vagolytic effects of digitalis have not been described. Antiadrenergic effects of digitalis on the sinus node have been suggested,[26,27] although the mechanism is unknown. Reflex-induced vagal inhibition has been excluded.[26] Ten Eick and Hoffman[22] showed that digitalis induced sinus bradycardia in cats, dogs and rabbits after vagal blockade or vagotomy, after beta adrenergic blockade or cardiac sympathectomy but not after combined parasympathetic and beta adrenergic blockade. These data confirm the vagal and antiadrenergic effects of digitalis on sinus rate and appear to exclude any significant direct effect of digitalis on the sinus node in at least three mammalian species.

Other data suggest that the actions of digitalis on the mammalian sinus rate might result from a skewed balance between the vagal and antiadrenergic effects and several contrasting effects rather than from the vagal and antiadrenergic effects alone. These additional effects, which appear to be less potent than the vagal and antiadrenergic effects in most mammals, include adrenergic stimulation[23,25,30] and possibly a direct positive chronotropic effect[31] not seen by Ten Eick and Hoffman.[22] The adrenergic stimulation occurs both by direct potentiation of impulses in sympathetic fibers[23,30] and by excitation of sympathetic preganglionic spinal neurons with resultant adrenal catecholamine secretion.[25] The catecholamine-releasing effect is greatly reduced by pentobarbital sodium anesthesia.[25] Direct stimulatory effects have been suggested because toxic doses of digitalis have generally been shown to accelerate rather than to decrease sinus rate[24,26,31-33] in both the innervated[24] and denervated[26] heart unless sinoatrial block appears.[34] Although Mendez et al.[26] interpreted such data to suggest a direct, possibly dose-related stimulatory action of digitalis on the sinus node that may exceed the antiadrenergic effects when sympathetic tone is low, only in the work of Bonke et al.,[31] in which sinus acceleration resulted from direct application of digitalis to the isolated sinoatrial node of the rabbit, could the adrenergic effects of adrenal catecholamine secretion[25] be excluded. If the vagal, antiadrenergic and adrenergic actions are balanced differently in man than in other mammals or if direct stimulatory effects occur with therapeutic doses of digitalis in man, the effects of digitalis on sinus rate in man could be explained.

Effects of digitalis on human sinoatrial node: In human studies, the effects of digitalis on sinus rate contrast with those in animal investigations. In subjects both with and without sinus nodal dysfunction, usually no change, less frequently a slight increase but thus far no decrease in sinus rate has been noted after digitalis (Table I).[7,11-13,17] The present study confirms the absence of a significant effect by digoxin on the sinus rate in most patients. This absence of sinus rate slowing in man as compared with animals, especially in subjects without sinus nodal dysfunction,[13,17] suggests that differences among species exist, that anesthetic agents or surgical trauma can affect the sinus nodal response to digitalis or less likely, that cardiac symptoms or disease affect the human sinus nodal response to digitalis even in the absence of sinus nodal dysfunction.

Digitalis effects with and without vagal blockade: To evaluate the mechanism of the effect of digitalis on human sinus nodal function, our study contrasted the action of digoxin after vagal blockade with its action without vagal blockade. In each subject, digoxin caused a decrease in sinus rate when given after atropine. This indicates an antiadrenergic or a direct suppressive effect of the drug, or both, in man. In light of this negative chronotropic response after atropine, it is surprising that in the presence of an intact, also negatively chronotropic vagal mechanism, digitalis does not cause a decrease in the sinus rate in man as it does in animals.

There are at least two possible although unproved explanations for this seemingly paradoxic finding. First, if adrenergic or positively chronotropic direct effects of digitalis occur in man, they may oppose any vagal or antiadrenergic effects and therefore prevent any decrease in the sinus rate in the basal state. However, if they are relatively weak, as in animals, the logic of Mendez et al.[26] would have to be utilized to account for the data; that is, these effects can only be manifest when sympathetic tone is low and vagal tone already high (as in the resting state), thereby minimizing any vagal or antiadrenergic actions of the drug. This may be especially true in some patients with the sick sinus syndrome.[35] Similar logic would have to be used to explain the decrease in the sinus rate caused by digoxin after vagal blockade, that is, if adrenergic or positive chronotropic direct effects are relatively weak compared with the positive chronotropic effect of withdrawing vagal inhibition, they may not be able to enhance sinus rate further whereas the ability of antiadrenergic effects to become manifest might be enhanced. However, the finding by Goodman et al.[17] that digitalis caused no change in sinus rate in six patients after cardiac transplantation suggests that digitalis has no direct effect on the sinus rate in man or that adrenal catecholamine release (although no other adrenergic effects) may not result from digitalis in man, or both, unless the aftereffects of surgical trauma or the recipient's underlying disease affect their manifestation. Second, it is possible that digitalis has vagolytic rather than vagomimetic effects in man in contrast to other species. This hypothesis has been suggested to explain the effects of ouabain on human atrial refractory periods by Dhingra et al.[13]

Digitalis and sinoatrial conduction time: In contrast to its effects on sinus rate, digitalis may prolong sinoatrial conduction time in man. Like Goodman et al.,[17] we found a mild but statistically insignificant increase in sinoatrial conduction time after the administration of digoxin, with the development of sinoatrial Wenckebach block in one patient who required a pacemaker for chronic digitalization. Other investiga-

tors[13,14] have found that the increase in sinoatrial conduction time after digitalis reached statistical significance (Table I).

In contrast to the variable findings in patients with unblocked vagi, digoxin increased sinoatrial conduction time significantly in 10 of our 11 patients after atropine as it did in the six patients of Goodman et al.[17] with a cardiac transplant. Although this increase may have resulted from an antiadrenergic action, the results in the latter six patients suggest a possible direct suppressive effect. As with sinus rate, the relatively mild response in the absence of vagal blockade or cardiac denervation is surprising and incompletely understood. The decrease in sinoatrial conduction time without suppression of the sinus rate when digitalis is given to a patient with intact autonomic function and the slowing of sinoatrial conduction time despite an unchanged sinus rate in patients with a cardiac transplant suggest that the glycosides have somewhat different effects on sinoatrial automaticity and conduction. This may reflect different effects on pacemaker P cells in the sinoatrial node and on the perinodal fiber.

Digitalis and sinus nodal recovery time: Unlike the data for sinus rate, there are no animal data to suggest how digitalis might affect sinus nodal recovery time after overdrive. Table I shows that in all studies to date except that of Goodman et al.[17] and in one case reported by Margolis et al.[6] digitalis caused corrected sinus recovery time to shorten in man. Because Goodman et al.[17] used unusually short and few paced cycle lengths, their data may not be comparable with those in the other studies. After atropine, we found that digoxin increased maximal corrected sinus recovery time in all patients. Therefore, the digoxin-induced shortening of corrected sinus recovery time in most patients in the absence of vagal blockade also seems surprising. Although such shortening might be related to those factors that keep the sinus rate from slowing as it does in animals with intact vagi, it is more likely related to suppression of sinoatrial conduction after digoxin. This antidromic action could cause sinus nodal entrance block during pacing or sinoatrial reentry after pacing. Either effect would be expected to shorten corrected sinus recovery time. Alternatively, the latter could also result from a decrease in overdrive "suppressibility" by digoxin.

Therapeutic implications: Regardless of the mechanism of action of digoxin on the sinus node, our data and those reviewed by Rubenstein et al.[2] suggest that most patients with sinus bradycardia or sick sinus syndrome can be given digitalis safely for therapy of cardiac arrhythmias or ventricular failure. Because exceptions do arise even in patients with normal corrected sinus recovery and sinoatrial conduction times and only mild sinus bradycardia before digitalis therapy[6,8,10] several observers[1,3,4] have suggested that all patients with sick sinus syndrome who require digitalis be given permanent pacemakers first. We do not agree. If the patient with sick sinus syndrome has symptoms that would benefit from pacemaker therapy independent of the indication for digitalis, such as syncope from sinoatrial arrest or atrioventricular block, then pacemaker insertion should undoubtedly be instituted. However, if the symptoms are due to a condition that may be controlled with digitalis, such as syncope from posttachycardia pauses in the bradycardia-tachycardia syndrome, or to ventricular failure, then in most cases digitalis can be given without a pacemaker. In this latter circumstance, the safest course to follow may be to evaluate the effects of digitalis on sinus nodal function by acute digitalization during an electrophysiologic study, using the study data to predict the long-term response to the drug. Our experience has shown that if severe increases in sinoatrial conduction time or corrected sinus recovery time are found, then insertion of a pacemaker is indicated. If no increases occur, as has been true in most patients described by ourselves and others,[7,11-17] then long-term treatment with oral digoxin may be given safely without prophylactic pacemaker insertion.

Thus, it appears that digitalis has extremely complex effects on sinus nodal function. It affects the sinus nodal firing rate through a variety of interactions with neuroadrenal modulatory mechanisms that may not be identical at all doses and in all species. The presence of direct effects on sinus nodal function has not been established with certainty in man, but these effects may be both present and different for automaticity and conduction. The clinical correlates of these complex actions are that the effects of digoxin on sinus nodal function are not entirely predictable in patients with sinus nodal dysfunction. In most patients, sinus cycle length will not change, sinoatrial conduction time may increase slightly and maximal corrected sinus recovery time will shorten. However, exceptions do occur perhaps in part because of the wide variation in baseline autonomic activity that exists in such patients. When the safety of digoxin administration in a patient with sinus nodal dysfunction is in question and other therapeutic interventions such as pacemaker insertion depend solely on the effects of its administration, acute digitalization during electrophysiologic testing of sinus nodal function may quickly and safely suggest the results to be expected during its long-term administration.

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Combined Therapy With Digoxin and Nitroprusside in Heart Failure Complicating Acute Myocardial Infarction

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The hemodynamic effects of digoxin plus nitroprusside were compared with those of nitroprusside alone in 11 patients with congestive heart failure complicating acute myocardial infarction. Hemodynamic measurements were made using a Swan-Ganz thermodilution catheter and a bedside thermodilution cardiac output computer. Patients received increasing doses of nitroprusside until mean arterial pressure decreased to 70 mm Hg or pulmonary arterial wedge pressure decreased to 16 mm Hg. The infusion rate of nitroprusside was then held constant for 120 minutes. After 30 minutes of constant nitroprusside infusion, 0.5 mg of digoxin was given intravenously. Hemodynamic measurements were obtained before treatment with nitroprusside and immediately before and 30, 60 and 90 minutes after the administration of digoxin.

Nitroprusside produced a significant decrease in pulmonary arterial wedge pressure (24 to 16 mm Hg), mean arterial pressure (92 to 85 mm Hg and systemic vascular resistance (1,816 to 1,480 dynes sec cm^{-5}) and a significant increase in cardiac index (2.19 to 2.51 liters/min per m^2). Ninety minutes after the administration of digoxin, cardiac index was further increased (2.51 to 28.2 liters/min per m^2, $P = 0.03$) and systemic vascular resistance was lower (1,480 to 1,320 dynes sec cm^{-5}, $P = 0.03$). Pulmonary arterial wedge pressure was not further decreased by the addition of digoxin. Thus, the addition of digoxin further increases cardiac output in patients with congestive heart failure complicating myocardial infarction who are receiving nitroprusside but does not produce any further decrease in pulmonary arterial wedge pressure.

The use of vasodilating agents in the treatment of congestive heart failure complicating acute myocardial infarction results in improved left ventricular function[1–5] and increased survival.[4,5] The vasodilator used most frequently in this situation is nitroprusside,[6] an agent that produces balanced dilatation in both the venous and arteriolar beds with a resultant decrease in pulmonary capillary wedge pressure and an increase in cardiac output.[7] However, in some patients, the level of cardiac output may remain low or pulmonary capillary wedge pressure high despite maximal vasodilator treatment. Because nitroprusside has no inotropic effect,[8] the addition of a positive inotropic agent should result in a further improvement in cardiac function in these patients.

Digitalis is the inotropic agent most commonly used to treat chronic congestive heart failure, but its role in the treatment of congestive heart failure complicating acute myocardial infarction remains controversial.[9] However, the weight of the available evidence suggests that digitalis improves ventricular performance in patients with acute myocardial infarction, particularly if sensitive measures of left ventricular function are used to detect this change.[10]

The present study was undertaken to determine whether the combination of a vasodilator (nitroprusside) and a positive inotropic agent (digoxin) would improve cardiac performance more than treatment with

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a vasodilator alone in patients with congestive heart failure complicating acute myocardial infarction.

Methods

Patients: The study population consisted of 11 patients with acute myocardial infarction. In all patients, myocardial infarction was documented by a history consistent with infarction, the development of pathologic Q waves in the electrocardiogram and an increase in serum creatine kinase with the appearance of the myocardial fraction of creatine kinase (CK MB) on electrophoresis. There were eight men and three women with a mean age of 57 years (range 36 to 68 years). The location of the infarction was anterior in eight patients and inferior in three. None of the 11 patients had ever taken digitalis or a vasodilator before this study. All were in Killip class II or III at the time of study. Continuous electrocardiographic monitoring in the coronary care unit was carried out on all patients during the period of this study.

Protocol: After informed consent had been obtained, a Swan-Ganz triple lumen thermodilution catheter was positioned in the pulmonary artery. Cardiac output was determined using 10 cc of iced saline solution and an Edwards Laboratories cardiac output computer, model 9510A. Each cardiac output was determined in triplicate. Arterial pressure was obtained directly via a radial artery cannula. All pressures were measured with Hewlett Packard model 1290C pressure transducers and model 78205B pressure modules. Mean pressures were obtained by electronic damping.

After baseline hemodynamic measurements were obtained, an infusion of nitroprusside was begun at 50 μg/min. The infusion rate was increased by 17 μg/min every 10 minutes until the mean arterial pressure was less than 70 mm Hg or the pulmonary capillary wedge pressure decreased to 16 mm Hg. The infusion rate was then held constant for the remainder of the study. After the infusion rate had been stabilized for 30 minutes, hemodynamic measurements were repeated. Digoxin, 0.5 mg, was then given intravenously over 30 seconds and the hemodynamic measurements were repeated 30, 60 and 90 minutes after administration of digoxin. No patient received any other hemodynamically active agent during this study. Only patients who completed the entire study within 48 hours of the onset of infarction are included in this report.

Hemodynamic variables were calculated using standard formulas. Statistical analysis was performed using a paired *t* test for small samples.

Results

The average dose of nitroprusside was 120 μg/min (range 50 to 280), and the average time from the onset of infarction to initiation of therapy was 9 hours (range 3 to 29). No patient had ventricular arrhythmias that required treatment after digoxin therapy.

Hemodynamic measurements (Table I): Before treatment, all patients had an elevated pulmonary capillary wedge pressure (mean 24 ± 3 mm Hg, range 21 to 30). The cardiac index was less than 2.5 liters/min per m^2 in 10 patients and in the 11th patient, it was in the low normal range (2.61 liters/min per m^2). Systemic vascular resistance was elevated in all patients (mean 1,860, dyne-cm/sec^5, range 1,520 to 2,320 dynes sec cm^{-5}). At maximal nitroprusside infusion, there was a significant decrease in mean arterial pressure, pulmonary capillary wedge pressure and systemic vascular resistance and a significant increase in cardiac index and stroke index. Stroke work index increased from 23 to 25 g-m/m^2, but the change was not significant ($P = 0.08$). Heart rate did not change. After digoxin administration, there was no further change in heart rate, mean arterial pressure, or pulmonary capillary wedge pressure. Cardiac index continued to rise, and 90 minutes after digoxin administration it was greater than with nitroprusside alone (2.51 versus 2.82 liters/min per m^2) ($P = 0.03$). Although nitroprusside alone did not result in a significant increase in stroke work index, 30 and 90 minutes after digoxin this variable was increased over control values (23 versus 27 g-m/m^2) ($P = 0.05$) but was not different from the stroke work index after nitroprusside alone (25 versus 27 g-m/m^2) ($P = 0.1$). Systemic vascular resistance, which decreased with nitroprusside therapy, continued to decline after digoxin administration, and 90 minutes after digoxin it was lower than with nitroprusside alone (1,480 versus 1,320 dynes sec cm^{-5}) ($P = 0.03$).

Analysis of hemodynamic changes (Fig. 1): Nitroprusside administration produced a decrease in pulmonary capillary wedge pressure and systemic vascular resistance in all patients. Ninety minutes after digoxin administration, pulmonary capillary wedge

TABLE I

Hemodynamic Data

	HR	MAP	PCWP	CI	SWI	SVR
C	94 ± 20	92 ± 11	24 ± 3	2.19 ± 0.33	23 ± 7	1816 ± 264
N	95 ± 17	85 ± 11*	16 ± 2†	2.51 ± 0.57*	25 ± 7	1480 ± 376†
D30	94 ± 18	86 ± 11*	16 ± 4†	2.63 ± 0.55‡	27 ± 8*	1432 ± 296†
D60	93 ± 16	84 ± 12*	17 ± 5†	2.60 ± 0.57†	26 ± 6	1424 ± 368†
D90	98 ± 19	83 ± 13*	17 ± 3†	2.82 ± 0.72†§	27 ± 9*	1320 ± 320†§

* Probability (P) < 0.05 versus control.
† $P < 0.001$ versus control.
‡ $P < 0.01$ versus control.
§ $P < 0.05$ versus nitroprusside.
Values are mean ± 1 standard deviation.
C = control data; CI = cardiac index (liters/min per m^2); D30, D60 and D90 = data 30, 60 and 90 minutes, respectively, after 0.5 mg of digoxin; HR = heart rate (beats/min); MAP = mean arterial pressure (mm Hg); N = data during constant nitroprusside infusion; PCWP = pulmonary capillary wedge pressure (mm Hg); SVR = systemic vascular resistance (dynes sec cm^{-5}); SWI = stroke work index (g-m/m^2).

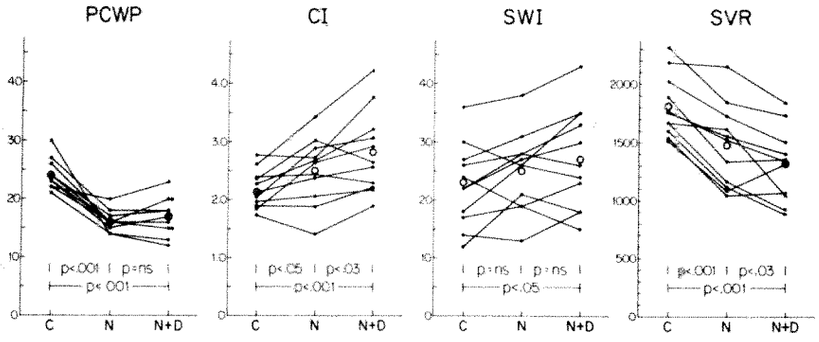


FIGURE 1. Individual and group data for pulmonary capillary wedge pressure (PCWP, mm Hg), cardiac index (CI, liters/min per m^2), stroke work index (SWI, g-m/m^2), and systemic vascular resistance (SVR, dynes sec cm^{-5}). The values shown were obtained during the control period (C), during constant nitroprusside infusion (N) and 90 minutes after the administration of digoxin (N + D). Mean values are indicated by **open circles.** ns = not significant (probability > 0.05); p = probability.

pressure remained unchanged in all patients, whereas in eight patients systemic vascular resistance had decreased further. Cardiac index increased from control values in 7 patients with nitroprusside alone and in 10 patients with nitroprusside plus digoxin. In 9 of 11 patients the cardiac index was greater with nitroprusside plus digoxin than with nitroprusside alone. In five patients, cardiac index remained less than 2.5 liters/min per m^2 after treatment with nitroprusside, and in four of these patients cardiac index increased further after digoxin. Six patients had a normal cardiac index after treatment with nitroprusside, and in five of these patients, cardiac index continued to improve after digoxin was added. Similarly, eight patients showed an increase in stroke work index with nitroprusside alone whereas nine showed an increase in stroke work index with nitroprusside plus digoxin. In seven patients, stroke work index was greater with nitroprusside plus digoxin than with nitroprusside alone.

Discussion

The three most important determinants of cardiac output are preload, afterload and the inotropic state of the myocardium.[11] Although the latter determinant, inotropic state, is important in both the normal and failing heart, the same cannot be said about ventricular loading because the normal heart is preload-dependent and afterload-independent, whereas the reverse is true for the failing heart as long as filling pressures remain elevated.[6] Although the dependence of cardiac output on afterload was appreciated by Patterson and Starling[12] in 1914, it was not until 1971 that Majid et al.[13] utilized this principle for therapeutic purposes. A substantial body of evidence has now been accumulated showing that vasodilators are effective in the treatment of chronic congestive heart failure[6,14–16] and acute congestive heart failure complicating acute myocardial infarction.[1–5] Although several vasodilators have been used, nitroprusside is the drug most frequently employed in the treatment of acute congestive heart failure.[6,14] This agent has a balanced effect in reducing both venous and arteriolar tone resulting in a decrease in ventricular filling pressures and an increase in cardiac output.[7] In the present study, all measures of cardiac performance improved after nitroprusside therapy whereas systemic vascular resistance and mean arterial pressure decreased. These results are consistent with those of previous studies on the use of nitroprusside in congestive heart failure after acute myocardial infarction.[1–5]

Digitalis in congestive heart failure complicating acute myocardial infarction: Because nitroprusside has no intrinsic inotropic properties, the combination of nitroprusside and a positive inotropic agent might be expected to improve cardiac function more than either agent alone. In chronic congestive heart failure, the use of nitroprusside plus dopamine produces a larger increase in cardiac index than either agent individually.[17,18] However, the usefulness of a positive inotropic agent, especially digitalis, in congestive heart failure complicating acute myocardial infarction remains controversial.[9,10] Numerous experimental[19,20] and clinical[21–23] studies have failed to show any increase in cardiac output or reduction in pulmonary capillary wedge pressure after the administration of digitalis in the presence of acute myocardial infarction. In part, these results are explained by the fact that in some of these studies little clinical or hemodynamic evidence of congestive heart failure was present before digitalization.[21,22] Because digitalis is known to have little or no effect on cardiac output or pulmonary capillary wedge pressure in the absence of congestive heart failure,[24] these results are not surprising. In the absence of congestive heart failure, the direct peripheral vasoconstrictor effects of digitalis may predominate, and the subsequent increase in ventricular afterload may actually cause a decrease in cardiac output and an increase in pulmonary capillary wedge pressure.[24,25] In patients with congestive heart failure complicating acute myocardial infarction, digitalis can produce an increase in cardiac index and a decrease in pulmonary capillary wedge pressure,[25–28] although these beneficial effects may not occur in all patients with congestive heart failure.[23] Rahimtoola et al.[28] showed that even in the absence of an increase in cardiac index or a decrease in pulmonary arterial wedge pressure, digitalis improves left ventricular function in patients with congestive heart failure after acute myocardial infarction. In this study the first derivative of left ventricular pressure (dP/dt) was significantly increased and the ratio of preejection period to left ventricular ejection time (PEP/LVET) significantly decreased after the admin-

istration of ouabain to patients with acute myocardial infarction and congestive heart failure.

Digoxin plus nitroprusside: Whatever the effects of digitalis alone in acute myocardial infarction, our study demonstrates that digoxin given to patients with heart failure who were already receiving nitroprusside produced a significant increase in cardiac index and stroke work index. This increase in cardiac index occurred whether or not the cardiac index had been normalized by nitroprusside therapy. Concomitant with this increase in cardiac index, systemic vascular resistance fell significantly from the level achieved with nitroprusside alone. Presumably, withdrawal of sympathetic tone occurred as cardiac output increased with a resultant decrease in systemic vascular resistance.[24] Although it is unlikely that such changes in cardiac index and systemic vascular resistance were spontaneous and unrelated to the administration of digoxin, this possibility cannot be excluded. However, in our experience patients receiving nitroprusside tend to have a stable hemodynamic pattern as long as the rate of infusion of the drug is kept constant.

Digitalis and cardiac output: The mechanism responsible for the increase in cardiac output after the administration of digitalis remains open to question. Maroko and Braunwald[29] have shown that an area of infarction is surrounded by a "border zone" of ischemic tissue, which in turn is surrounded by normally perfused myocardium. In experimental infarction Banka et al.[30] concluded that digitalis preparations retain a positive inotropic effect on both the normal and border zones but have no effect on the central zone of infarction. In that study both the total tension developed and the rate of tension development in the normal and border zones were increased by the administration of digoxin. Previously, Sarnoff et al.[31] demonstrated that digitalis increased myocardial contractility in the isolated heart preparation even when coronary flow was reduced to 30 percent of control values. Thus, the increase in cardiac output in our patients could be due to the positive inotropic effect of digitalis. However, another explanation is possible. When given to dogs with acute myocardial infarction and congestive heart failure, intravenous digitalis increased coronary collateral blood flow to ischemic zones.[32] This increase in coronary flow was accompanied by a marked decrease in ischemic S-T segment elevation. Similar changes in coronary flow to ischemic zones and electrocardiographic signs of ischemic injury were demonstrated by Vatner et al.[33] They also showed that these changes in coronary blood flow are accompanied by an improvement in overall left ventricular function and in contraction characteristics of the ischemic zone. Finally, when given to patients with acute myocardial infarction and congestive heart failure, digitalis decreased final infarct size as measured by serum creatine kinase accumulation.[34] These data suggest that digitalis may improve left ventricular function in acute myocardial infarction by decreasing myocardial ischemia with a resultant improvement in the contraction characteristics of the ischemic zone rather than by its positive inotropic effect.

Digitalis and pulmonary capillary wedge pressure: Nitroprusside produced a significant decrease in pulmonary capillary wedge pressure from 24 to 17 mm Hg, but the addition of digoxin did not result in any further decrease in this pressure. The reasons for this failure of digoxin to decrease pulmonary capillary wedge pressure further are not clear. Both digitalis and nitroprusside decrease ventricular filling pressures by increasing venous capacitance and decreasing venous return to the heart. In the case of nitroprusside, this is a direct effect of the drug,[8] whereas with digitalis, venous relaxation is due to a decrease in sympathetic tone consequent to an increase in cardiac output.[24] The decrease in systemic vascular resistance in our patients after the administration of digoxin suggests that sympathetic withdrawal did occur. It may be that in the presence of the direct venous dilating effects of nitroprusside, a further decrease in venous tone could not occur despite decreased sympathetic stimulation and, therefore, pulmonary capillary wedge pressure did not decrease after treatment with digitalis. It is also possible that the change in cardiac volume produced by digoxin was too small to produce a decrease in left ventricular end-diastolic pressure because it is known that in the postinfarction state, ventricular compliance may be greatly altered.[35]

Clinical implications: The combination of nitroprusside and digoxin produced a greater increase in cardiac index and stroke work index and a greater fall in systemic vascular resistance than were produced by nitroprusside alone when given to patients with congestive heart failure in the early stages of acute myocardial infarction. This further increase in cardiac index occurred whether or not cardiac index had been normalized by nitroprusside. Treatment with nitroprusside plus digoxin did not result in any greater decrease in pulmonary capillary wedge pressure than treatment with nitroprusside alone. Therefore, this combination of a positive inotropic agent and a vasodilator may be useful in the treatment of congestive heart failure complicating acute myocardial infarction.

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Lack of Ouabain Effect on Pacing-Induced Myocardial Ischemia In Patients With Coronary Artery Disease

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Sixteen patients with significant two and three vessel coronary artery disease but without clinical congestive heart failure were studied during rapid atrial pacing before and after infusion of 0.015 mg/kg of ouabain. Seven patients with a decreased (less than 50 percent) ejection fraction and nine patients with a normal ejection fraction had a significant ($P < 0.05$) increase in resting arterial systolic pressure after the administration of ouabain. However, resting values for coronary sinus flow, coronary vascular resistance, myocardial oxygen consumption and myocardial lactate extraction did not change significantly in either group. During pacing, patients with a decreased ejection fraction demonstrated more ischemia than patients with a normal ejection fraction; however, the administration of ouabain did not significantly alter pacing-related changes in coronary sinus flow, myocardial oxygen consumption, myocardial lactate extraction, ischemic electrocardiographic changes or onset of chest pain in either group. The administration of ouabain has a negligible effect on coronary hemodynamics, myocardial metabolism or clinical signs of ischemia in patients with coronary artery disease with normal or abnormal left ventricular function.

Although digitalis is used frequently in patients with coronary artery disease, its net effect on the relation between myocardial oxygen supply and demand remains unclear. By its inotropic action, digitalis increases myocardial oxygen demand[1]; at the same time, it may limit oxygen supply by direct coronary constriction.[2] On the other hand, by decreasing heart rate and ventricular chamber size, digitalis may decrease myocardial oxygen requirements and improve oxygen delivery to the subendocardium by reducing the ventricular filling pressure.[3]

Experimental studies[4] suggest that left ventricular function may be an important determinant of how digitalis alters myocardial oxygen supply and demand relations. We undertook this study to investigate how left ventricular performance might influence the acute effects of digitalis on coronary hemodynamics, myocardial metabolism and clinical signs of ischemia during rapid atrial pacing in patients with significant coronary artery disease.

Methods

Patients: Patients were selected for study on the basis of angiographically proved coronary artery disease and the absence of clinical heart failure severe enough to have required digitalis therapy in the past. Sixteen men, aged 42 to 63 years (average 53.5), were studied. All patients had a clinical diagnosis of angina pectoris, and seven had electrocardiographic evidence of previous myocardial infarction. All patients had normal sinus rhythm. The study was performed in a specially equipped unit adjacent to the coronary care unit. Informed consent was obtained from each patient.

Procedures: Arterial systolic, mean and diastolic pressures were measured with a Statham 23DB transducer after percutaneous insertion of a cannula into

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the radial or brachial artery. Coronary sinus flow was measured utilizing the continuous thermal dilution technique described by Ganz et al.[5] In our laboratory, flows determined in vitro utilizing this technique correlated well ($r = 0.949$) with directly measured flows of 50 to 450 cc/min delivered by an adjustable sigma motor pump into a circuit of synthetic tubing. After insertion of the thermistor catheter, its position was verified by injecting contrast material to outline the coronary sinus. To maintain a stable catheter position, the external thermistor was positioned well beyond the mouth of the coronary sinus. In this location, flow measurement and blood sampling are primarily reflections of blood supply to the anterolateral left ventricle. Although reflux of right atrial blood into the coronary sinus during rapid atrial pacing has been reported to result in erroneously elevated coronary sinus flow values,[6] mean coronary sinus oxygen saturation in our patients was essentially the same before and during pacing (26.3 and 26.9 percent, respectively). Although reflux of right atrial blood could conceivably have been masked by an equivalent true decrease in coronary sinus oxygen saturation, we think it unlikely that this occurred.

Coronary vascular resistance was calculated as the ratio of mean arterial pressure to coronary sinus flow. Atrial pacing was performed from the same catheter which was also equipped with bipolar pacing electrodes. Heart rate and S-T segment displacement were monitored throughout the study from a single calibrated electrocardiographic lead (V_5). Double product was calculated as the product of arterial systolic pressure and heart rate. Recordings were made on a Hewlett-Packard photographic recorder at variable paper speeds. Arterial and coronary sinus lactate concentrations were measured with enzymatic techniques.[7] Myocardial lactate extraction was calculated as (arterial lactate minus coronary sinus lactate/arterial lactate) times 100. Arterial and coronary sinus blood oxygen in percent saturation was measured with an American Optical oximeter. Myocardial oxygen consumption was calculated as coronary sinus flow times (arterial oxygen minus coronary sinus oxygen).

Atrial pacing before and after ouabain: Before atrial pacing, two control measurements were obtained 15 minutes apart and averaged to yield a single control value (C_1). Differences between the two control measurements (mean ± standard error of the mean) were 3.0 ± 6.0 cc/min for coronary sinus flow, 9.2 ± 6.2 percent for myocardial lactate extraction and 1.2 ± 1.3 percent for arterial oxygen saturation minus coronary sinus oxygen saturation; these differences were not significant. After control measurements, atrial pacing was started and the pacing rate increased every 1 to 2 minutes until chest pain appeared. In two patients who did not have chest pain during pacing, the maximal heart rate achieved was 160 beats/min in both. Measurements were repeated at the peak pacing rate (P_1) and pacing was then discontinued. To avoid baseline shift due to atrial depolarization during pacing, measurement of S-T segment change was made from the first few sinus beats after termination of pacing. A flat or downward sloping S-T depression of 0.1 mv or greater was considered "ischemic."

After this initial pacing period, the patient was allowed to return to a basal state for approximately 30 minutes. Ouabain, 0.015 mg/kg in 20 cc of saline solution, was then infused over a 10 to 15 minute interval. The total dose of ouabain given ranged from 0.7 to 1.4 mg (average 1.1 mg). Measurements were repeated 15 and 30 minutes after completion of ouabain infusion and averaged for a single second control value (C_2). Atrial pacing was then repeated (P_2), with measurements obtained as previously described. When necessary, atropine, 0.5 to 1.0 mg intravenously, was given during pacing to achieve an adequate ventricular response. Three patients received atropine during both pacing periods, one patient during the first pacing period only and five patients during the second (postouabain) pacing period only.

Statistical significance was determined with the Student's t test for paired numerical data. Probability (P) values above 0.05 were considered not significant.

Results

At the time of coronary arteriography, all 16 patients had significant obstruction (70 percent or greater obstruction of the cross-sectional area) of two (10 patients) or three (6 patients) major coronary vessels. Left ventricular ejection fraction was measured in each patient. In nine patients, ejection fraction was normal (50 percent or greater), averaging 68 percent (range 50 to 91 percent). In the remaining seven patients, ejection fraction was less than 50 percent, averaging 34 percent (range 20 to 49 percent).

Hemodynamic Data

Heart rate: In the nine patients with a normal ejection fraction, heart rate increased with pacing from 71 ± 3 to 145 ± 6 beats/min before administration of ouabain and from 74 ± 4 to 141 ± 6 beats/min after ouabain. In the seven patients with a decreased ejection fraction, heart rate increased with pacing from 76 ± 3 to 149 ± 5 beats/min before administration of ouabain and from 79 ± 4 to 140 ± 5 beats/min after ouabain. The values for resting and paced heart rates were not significantly different before and after ouabain in either group of patients.

Arterial pressure: In the nine patients with a normal ejection fraction, arterial systolic pressure was 134 ± 10 mm Hg at rest and 132 ± 14 during the first pacing period. After ouabain, the resting value increased significantly ($P < 0.05$) to 143 ± 9 mm Hg. With pacing, arterial systolic pressure was 140 ± 15 mm Hg and was not significantly different from the value during pacing before ouabain. Before ouabain, mean arterial pressure and arterial diastolic pressure were increased during pacing from 91 ± 5 and 67 ± 3 mm Hg to 97 ± 8 and 78 ± 5 mm Hg, respectively. Ouabain did not significantly alter these pressures either at rest or during pacing, mean arterial pressure increasing from 94 ± 4 to 99 ± 10 mm Hg and arterial diastolic pressure increasing from 71 ± 2 to 81 ± 7 mm Hg.

In the seven patients with a reduced ejection fraction, arterial systolic pressure was 124 ± 5 mm Hg at rest and 151 ± 11 during pacing before ouabain. After ouabain, resting arterial systolic pressure increased to 141 ± 5 mm Hg ($P < 0.02$). During the second pacing period, arterial systolic pressure was 158 ± 11 mm Hg, which was not significantly different from the value during pacing before ouabain. During the first control period, mean arterial pressure and arterial diastolic pressure were 91 ± 3 and 71 ± 3 mm Hg at rest, increasing to 114 ± 7 and 94 ± 5 mm Hg, respectively, during pacing. After ouabain, these pressures were similar, averaging 95 ± 4 and 74 ± 3 mm Hg and increasing to 114 ± 6 and 94 ± 6 mm Hg, respectively, during pacing.

Double product: In the nine patients with a normal ejection fraction, the double product before ouabain was 9500 ± 700 mm Hg × beats/min, increasing to 18,700 ± 1,500 with pacing. After ouabain, the resting double product was significantly increased ($P < 0.05$), averaging 10,400 ± 600 mm Hg × beats/min. During pacing after ouabain, double product increased to 19,300 ± 1,700 mm Hg × beats/min, a value not significantly different from that during pacing before ouabain. In the seven patients with a reduced ejection fraction, the double product before ouabain was 10,400 ± 700 mm Hg × beats/min and increased to 22,400 ± 1,700 during pacing. After ouabain, resting double product was 11,100 ± 800 mm Hg × beats/min and increased to 22,000 ± 1,500 during pacing. Neither resting nor paced double product after ouabain was significantly changed from pre-ouabain values.

Coronary sinus flow (Fig. 1): Patients with a normal ejection fraction had resting coronary sinus flow averaging 121 ± 18 cc/min, which increased to 179 ± 13 during pacing. After ouabain, coronary sinus flow at rest was 112 ± 10 cc/min, increasing to 158 ± 8 with pacing. Patients with an abnormal ejection fraction had coronary sinus flow averaging 99 ± 17 cc/min at rest, increasing to 223 ± 44 with pacing. After ouabain, coronary sinus flow was 124 ± 27 cc/min at rest, increasing to 281 ± 79 during pacing. The values for coronary sinus flow at rest and during pacing did not differ significantly before as compared with after ouabain.

Coronary vascular resistance (Fig. 2): Patients with a normal ejection fraction had a reduction in coronary vascular resistance with pacing from 0.82 ± 0.09 to 0.62 ± 0.10 units. After ouabain, coronary vascular resistance decreased with pacing from 0.90 ± 0.11 to 0.68 ± 0.06 units. Coronary vascular resistance values at rest and during pacing were not significantly different before and after ouabain. Patients with a reduced ejection fraction had a resting coronary vascular resistance averaging 1.25 ± 0.40 units, which fell to 0.59 ± 0.11 units during pacing. After ouabain, resting coronary vascular resistance was 1.06 ± 0.31 units (difference not significant). During pacing, coronary vascular resistance fell to 0.52 ± 0.10 units and was lower in each of the six patients than it had been before ouabain ($P < 0.05$).

Arterial-coronary sinus oxygen difference: Patients with a normal ejection fraction had an arterial-coronary sinus oxygen difference of 68 ± 2 percent at rest and 70 ± 2 during pacing. After ouabain, these values were essentially the same, averaging 69 ± 2 percent at rest and 70 ± 1 with pacing. In patients with a reduced ejection fraction, arterial venous oxygen difference before ouabain was 71 ± 1 percent at rest and 72 ± 2 during pacing. After ouabain, the respective values were 73 ± 2 percent and 74 ± 1 (difference not significant).

Myocardial oxygen consumption (Fig. 3): Because hemoglobin was not measured, myocardial oxygen consumption was expressed as percent change from control value rather than as cc/min. In patients with a normal ejection fraction, myocardial oxygen consumption increased by 55 ± 10 percent during the initial pacing period. After ouabain, resting myocardial oxygen consumption was 2.5 ± 10 percent above initial control values (difference not significant). During the second pacing period, myocardial oxygen consumption increased by 46 ± 16 percent and was not significantly different from the value during the first pacing period. In patients with a reduced ejection fraction myocardial oxygen consumption increased by 112 ± 32 percent during the first pacing period. After ouabain, resting

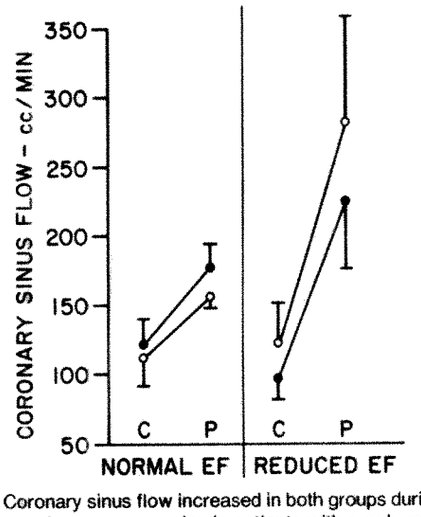


FIGURE 1. Coronary sinus flow increased in both groups during pacing with the greater increase occurring in patients with a reduced ejection fraction (EF). Although in both groups of patients, coronary sinus flow at rest (C) and during pacing (P) was higher after ouabain (**open circles**) than before ouabain (**closed circles**), the differences were not statistically significant.

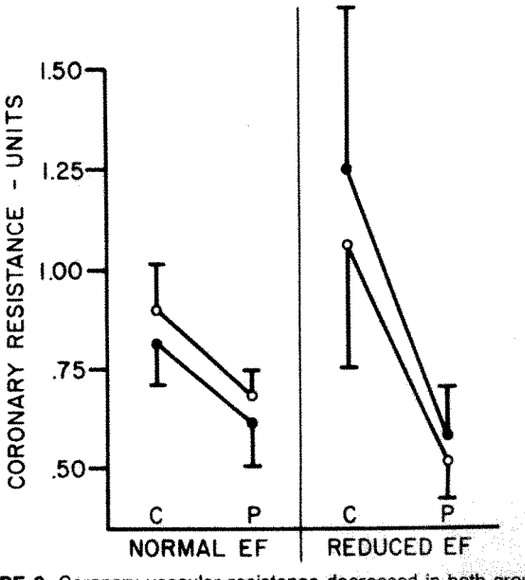


FIGURE 2. Coronary vascular resistance decreased in both groups during pacing. Ouabain had virtually no effect on the reduction of coronary resistance in response to increased metabolic needs. Symbols and abbreviations as in Figure 1.

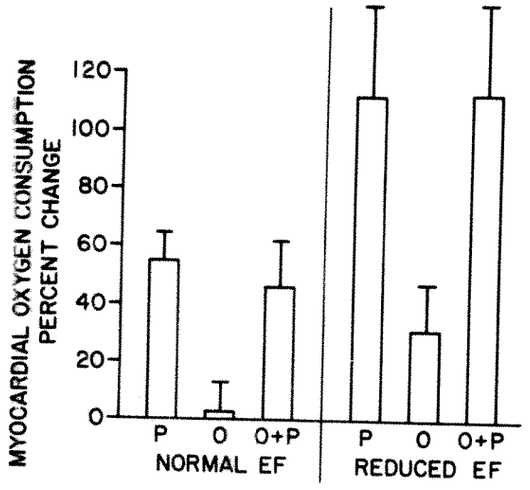


FIGURE 3. Percent change in myocardial oxygen consumption before and after ouabain. In patients with a normal ejection fraction (EF), similar increases in myocardial oxygen consumption occurred during pacing before (P) and after (O+P) ouabain; ouabain alone (O) had negligible effect on myocardial oxygen consumption. Patients with a reduced ejection fraction had larger increases in myocardial oxygen consumption during pacing than patients with normal ejection fraction but these increases were also similar before and after ouabain. Ouabain alone increased myocardial oxygen consumption in these patients, but the increase (31 ± 16 percent) was not statistically significant.

myocardial oxygen consumption increased by 31 ± 16 percent, but this difference was not significant. During the second pacing period, myocardial oxygen consumption increased by 113 ± 30 percent, which was not significantly different from the increase during pacing before ouabain.

Myocardial lactate extraction (Fig. 4): Eight of nine patients with a normal ejection fraction had normal (greater than 10 percent) myocardial lactate extraction at rest (average 35 ± 4 percent). With pacing, myocardial lactate extraction decreased to 16 ± 5 percent and was 10 percent or less in three patients. After ouabain, resting myocardial lactate extraction averaged 24 ± 5 percent (difference not significant) and was abnormal in three patients. During the second pacing period, myocardial lactate extraction again averaged 16 ± 6 percent (difference not significant) and was abnormal in three patients, two of whom had abnormal myocardial lactate extraction during the first pacing period. All patients with a reduced ejection fraction had normal values for resting myocardial lactate extraction, averaging 23 ± 5 percent. During pacing, myocardial lactate extraction became abnormal in five of the seven patients, averaging −1 ± 15 percent. After ouabain, resting myocardial lactate extraction was again normal in all patients, averaging 33 ± 8 percent. During pacing after ouabain, myocardial lactate extraction again became abnormal in the same five patients who had abnormal myocardial lactate extraction with pacing before ouabain. Average myocardial lactate extraction was −0.4 ± 16 percent and was not significantly different from that during the initial pacing period.

Electrocardiographic and Clinical Observations

Ischemic S-T segment changes developed during pacing in five of the eight patients with a normal ejection fraction. (Electrocardiographic changes in the ninth patient could not be interpreted because of left bundle branch block.) Average S-T depression was 0.13 ± 0.05 mv. After ouabain, no patient had changes in the resting electrocardiogram. During pacing, four of the five patients who had previously had ischemic S-T depression during pacing again had ischemic changes, with an average for the eight patients of 0.14 ± 0.05 mv depression (difference not significant). Five of the seven patients with an abnormal ejection fraction had ischemic S-T segment depression during the first pacing period, averaging 0.19 ± 0.06 mv. After ouabain, the resting electrocardiogram was again unchanged. During the second pacing period, four of the five patients who had ischemic changes during the first pacing period again had ischemic changes as did one additional patient. Average S-T segment depression was 0.16 ± 0.05 mv (difference not significant).

Chest pain during pacing developed in eight of the nine patients with a normal ejection fraction before ouabain and in all nine patients after ouabain. Six of the seven patients with an abnormal ejection fraction had chest pain during pacing both before and after ouabain. No patient in either group had chest pain at rest after ouabain.

Discussion

This study was undertaken to examine the acute effects of digitalis on coronary hemodynamics, myocardial metabolism and clinical manifestations of pacing-induced ischemia. It was postulated that the effects of digitalis might be different in patients with and without impaired left ventricular function and, for this reason, we analyzed our results separately for patients with a left ventricular ejection fraction above and below 50 percent. In examining our results, two facts became apparent: (1) The nine patients with a normal ejection fraction responded differently to pacing than did the seven patients with a reduced ejection fraction; and (2) in neither group of patients did ouabain administration significantly alter the hemodynamic, metabolic or clinical response to pacing.

Left ventricular function and response to pacing: Although the purpose of our study was not directed toward assessing how left ventricular function influenced the response to pacing, the difference we observed between the two groups of patients deserves comment. This difference was characterized by sizable increases in arterial systolic pressure, coronary sinus flow and myocardial oxygen consumption and decreases in myocardial lactate extraction in patients with abnormal ejection fraction, even though the increases in heart rate during pacing were similar for both groups of patients. Part of this difference may have been due to more advanced coronary artery disease in the seven patients with a reduced ejection fraction, of whom five had triple vessel disease compared with only one of the nine patients with normal ejection fraction. The re-

maining patients in each group had two vessel disease. We[8] previously reported a close correlation between pacing-induced elevation of arterial systolic pressure and other evidence of myocardial ischemia. The increase in arterial systolic pressure observed during pacing in our patients with a reduced ejection fraction coupled with the greater decrease in lactate extraction suggests that, as a group, these patients had more ischemia during pacing than did the nine patients with a normal ejection fraction. Impaired ventricular emptying plus increased arterial systolic pressure probably lead to larger increases in myocardial oxygen requirements, and these factors may explain the greater increase in coronary sinus flow and myocardial oxygen consumption observed during pacing in our patients with a reduced ejection fraction. In spite of the different responses to pacing by our two groups, the effects of ouabain both at rest and during atrial pacing were not significantly different in these groups.

Hemodynamic effects of digitalis: Acute administration of digitalis can exert several effects that influence myocardial oxygen supply or demand, or both. The direct vascular action of digitalis is primarily vasoconstrictive involving both arterioles and venules.[9] In our patients, resting arterial systolic pressure was significantly increased after ouabain. We did not measure cardiac output and therefore cannot say if the increase in arterial systolic pressure we observed after ouabain was due to an increase in systemic-vascular resistance or to its inotropic effects. Although rapid injection of ouabain is known to exert potentially dangerous increases in systemic resistance,[10] intravenous administration over 15 minutes (as was done in our patients) has been shown by DeMots et al.[11] not to result in significantly increased systemic-vascular resistance after 30 minutes.

Digitalis and coronary blood flow: The direct effects of digitalis on coronary blood flow and its distribution may also be important. Experimental studies[2] have shown that digitalis can cause alpha adrenergically mediated coronary constriction even in the presence of myocardial ischemia. Additional studies[12] suggest that digitalis tends to redistribute myocardial blood flow from the subendocardium to the subepicardium but that this effect may be the result of an increase in left ventricular systolic pressure. In contrast, Hamilton et al.[13] were unable to demonstrate significant effects of digoxin on myocardial thallium-201 uptake in conscious dogs.

The effects of ouabain on resting coronary blood flow have been studied by DeMots et al.,[14] who measured global coronary flow using xenon-133 in 11 patients with severe coronary artery disease but without congestive heart failure. No significant changes were observed immediately or 30 or 60 minutes after a 15 minute infusion of ouabain given in a dose of 0.015 mg/kg. A later similar study by these investigators[11] using coronary sinus flow measurements also failed to show significant changes in either coronary sinus flow or coronary vascular resistance 30 minutes after ouabain infusion, although a significant decrease in coronary sinus flow was present 2 minutes after a bolus injection of ouabain. These studies confirm our own results, which showed no significant effect of ouabain infusion on resting coronary sinus flow in patients with coronary artery disease but without congestive heart failure. Likewise, neither their study nor our own showed any significant effect of ouabain infusion on resting myocardial lactate extraction in patients with coronary artery disease.

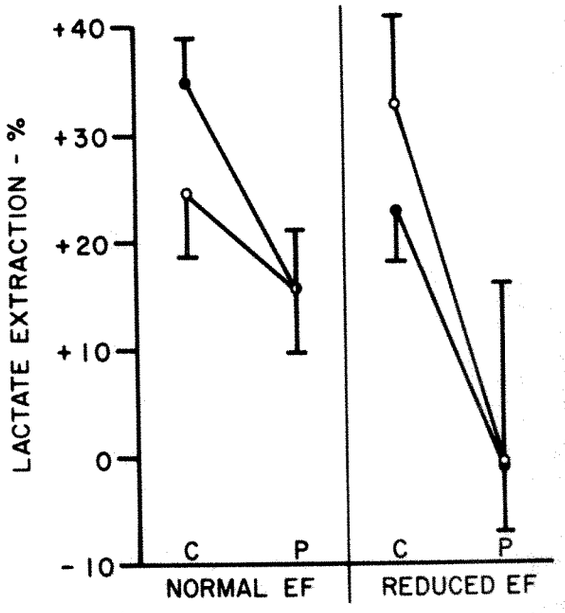


FIGURE 4. Myocardial lactate extraction was normal (greater than 10 percent) at rest in both patient groups and was not significantly affected by ouabain. During pacing, myocardial lactate extraction decreased more in the patients with a reduced ejection fraction, and mean myocardial lactate extraction became abnormal; however, in neither group did administration of ouabain have significant effects on myocardial lactate extraction during pacing. Symbols and abbreviations as in Figure 1.

Digitalis and myocardial ischemia: Although ouabain infusion appears to have negligible effects on resting coronary hemodynamics and myocardial lactate metabolism, its effects on myocardial ischemia during stress when myocardial oxygen requirements are increased could be important. Glancy et al.[15] studied the effects of ouabain (0.01 mg/kg) during supine bicycle exercise in 14 patients with coronary artery disease while measuring left ventricular pressure and cardiac output. Hemodynamic improvement after ouabain occurred in a few patients at rest and in 12 of 14 during exercise. In spite of this improvement, neither exercise tolerance nor pressure-rate product at onset of angina was altered. Higgs et al.[16] made similar measurements during rapid atrial pacing in 11 patients with coronary artery disease and reached identical conclusions, finding that ouabain did not delay or prevent the onset of angina in spite of hemodynamic improvement after its administration.

Ferlinz et al.[17] performed studies during atrial pacing before and after administration of ouabain in a dose of

0.07 mg/kg in 15 patients with coronary artery disease who did not have congestive heart failure. Resting coronary sinus flow and myocardial oxygen consumption were significantly increased after ouabain; however, lactate production and angina did not develop. During pacing, similar increases in coronary sinus flow and myocardial oxygen consumption and decreases in lactate extraction occurred before and after ouabain. Our results are consistent with those cited. In addition, we showed that the absence of ouabain effect on coronary sinus flow, lactate metabolism and electrocardiographic evidence of myocardial ischemia during rapid atrial pacing applies equally to patients with and without impairment of left ventricular function. However, we do not know whether results would have been similar if we had studied patients with clinical congestive heart failure.

Therapeutic implications: At times, digitalis therapy is required for control or prevention of supraventricular arrhythmias in patients with coronary artery disease but without clinical heart failure. Although some investigators have warned that digitalis might increase myocardial ischemia and result in worsening angina in such patients, our studies as well as those of others suggest that there is little likelihood that this will occur when the drug is used in modest doses. On the other hand, in the absence of clinical heart failure, we can find no justification from our data for the routine use of digitalis in patients with coronary artery disease and a reduced ejection fraction.

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Effects of Digitalis on Normal and Abnormal Left Ventricular Segmental Dynamics

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To study the effects of digoxin on regional left ventricular performance, continuous ventricular dynamics were assessed in nine patients with stable coronary disease. Computer-assisted analysis of the fluoroscopic motion of surgically implanted mid wall myocardial markers was used. The markers define six minor ventricular radii and outline the left ventricle. One and one-half hours after administration of 1 mg of intravenous digoxin, mean velocity of circumferential fiber shortening for all segments increased 19 percent, from 0.67 ± 0.06 to 0.78 ± 0.06 circumference/sec ($P < 0.01$) and ejection fraction increased 4.5 percent, from 0.50 ± 0.03 to 0.53 ± 0.03 ($P < 0.05$). Segmental velocity of circumferential fiber shortening, total segmental shortening and early segmental systolic shortening increased in 83 percent to 91 percent of normal segments, depending on which index was used. Only 45 to 55 percent of initially abnormal segments benefited from digoxin. In general, segmental dyssynergy increased even when net ventricular function was enhanced. These results suggest that in patients with chronic left ventricular contraction abnormalities due to coronary disease, deterioration of performance in abnormal regions after administration of digoxin may result from increased stress imposed by increased afterload and by improved segmental dynamics in more normal areas.

Studies that evaluate the influence of coronary artery disease on ventricular response to drugs such as digitalis have generally compared the responses of patients with coronary artery disease with results obtained from normal persons.[1–5] Although measures of ventricular function, such as ejection fraction and left ventricular end-diastolic pressure, provide a composite index of ventricular integrity, they do not quantitate the effects of localized contraction abnormalities on drug response. The response of regional left ventricular motion to drugs can be analyzed from left ventricular angiograms; however, multiple contrast injections are rarely performed in drug studies and segmental analysis is limited by problems of boundary recognition. We[6] previously published a study using myocardial marker measurements of velocity of circumferential fiber shortening and ejection fraction that showed improvement in global left ventricular function after intravenous and oral digoxin administration. This study extends those observations to assess the effects of intravenous digoxin on the performance of individual vantricular segments and points out differential responses of hypokinetic and normal segments.

Methods

Patient Selection

Nine patients, aged 41 to 60 years, who had had coronary bypass graft surgery 4 to 9 months earlier, participated in this study. At the time of cardiac surgery, each patient had seven tantalum coils (1.5 mm by 0.6 mm) implanted at a depth of 5 mm into the left ventricular wall (Fig. 1), so as to outline the left ventricular

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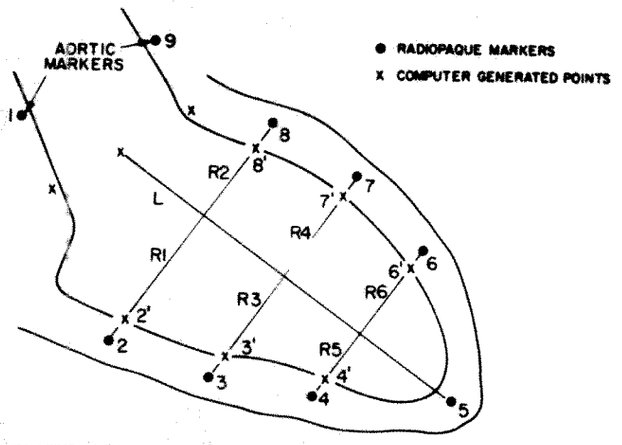


FIGURE 1. Distribution of myocardial markers within the left ventricular wall as viewed in the 30° right anterior oblique projection. (Modified with permission of Ingels et al.[7] and the American Heart Association, Inc.)

cavity as seen in the 30° right anterior oblique projection. In addition to the one apical, three anterior and three inferior markers, two tantalum clips were fixed to the aorta 3 cm above the level of the aortic valve to identify it on subsequent fluoroscopy. The patients gave informed consent at the time intramyocardial markers were placed and again for this specific study.

Baseline data included a physical examination, an electrocardiogram, and determinations of serum electrolyte and blood urea nitrogen. All patients were free of clinically evident congestive heart failure and none was using digitalis. Two were receiving diuretic drugs for hypertension, and two patients had mild angina pectoris. Three of the nine patients had electrocardiographic evidence of prior infarction and six had segmental wall motion abnormalities on preoperative left ventricular angiography (Table I). None of the nine patients had evidence of postoperative infarction, and all were free of angina. Myocardial markers were positioned in the prescribed manner so that areas of infarction and normal and abnormal wall motion were tagged.

Study Protocol

Ventricular function was evaluated with fluoroscopic assessment of the motion of the intramyocardial markers with the patient lying in the 30° right anterior oblique projection.[7] Recordings were made on a video disc at 30 frames/sec during suspended mid inspiration. Particular care was taken to avoid Valsalva maneuvers. Prior to fluoroscopic recording, each patient rested in the radiographic cradle for a minimum of 10 minutes or until heart rate and blood pressure were stable. A control sequence of four to nine beats was then recorded. After recording of control fluoroscopy, 1 mg of digoxin in 2 cc of dextrose solution was given intravenously over a period of 15 minutes. Fluoroscopic measurements were repeated 1.5 hours later. No untoward effects of the short-term digoxin administration were noted.

Data Computation and Analysis

A light-pen computer system was used to digitize the data obtained from frame by frame playback of the video disc.[7] Dimensional calibration was provided by fluoroscopy of a radiopaque grid placed at an echographically predetermined height above the tabletop.[8] End-diastolic frames were identified from the R wave of the electrocardiogram, which was superimposed on the video frames at the time of recording. Digitized data were transmitted to a CDC-6400 computer which provided both numerical outputs and plotted data using a CDC-280 microfilm graphic unit.

Instantaneous left ventricular volumes were calculated from the area circumscribed by lines connecting each patient's marker coordinates using the single plane area-length method of Sandler and Dodge.[9] Because a volume of muscle is included within the marker silhouette (because of mid wall placement), a correction factor previously derived from comparison with simultaneous contrast ventriculograms and marker recordings was used.[10] End-diastolic and end-systolic volumes were defined as *maximums* and *minimums*, respectively, of the left ventricular volume versus time curves for each beat, and stroke volume was calculated as the difference between end-diastolic and end-systolic volume. Cardiac output and ejection fraction were calculated from the end-diastolic, end-systolic and stroke volumes. The long axis was computed for each frame using the mid point of the aortic valve plane and the

TABLE I

Sites of Segmental Abnormality

Case no.	Site of Prior Infarct on ECG*	Site of Pre-op Ventriculographic Segmental Abnormality (RAO view)	Major Coronary Vessels With >80% Stenosis	Postoperative Marker Analysis: Location of Segments With Abnormal Baseline Dynamics		
				Total Shortening† (<12%)	Early Shortening* (<1%)	V_{CF}* (<0.35)
1	Inferior	Inferior	RCA, LAD	Normal	Normal	Normal
2	0	Anterior	LAD	Anterior	Anterior	Anterior
3	Inferior	Inferior	RCA, LAD	Inferior	Inferior	Inferior
4	Anterior	Anterior	LAD	Anterior	Anterior	Anterior
5	0	Inferior	LAD, LCx	Anterior	Anterior	Anterior
6	0	Inferior	LCx, RCA	Normal	Normal	Normal
7	0	0	RCA, LAD	Normal	Anterior	Anterior
8	0	0	LAD	Normal	Anterior	Anterior
9	0	0	LAD	Normal	Anterior	Normal

* Inferior = pathologic Q waves in leads II, III, avf; anterior = pathologic Q waves in leads V_1 to V_5.
† Anterior = segments 2, 4, 6; inferior = segments 1, 3, 5.
ECG = electrocardiography; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; normal = normal segmental index; Pre-op = preoperative; RAO = right anterior oblique; RCA = right coronary artery; V_{CF} = velocity of circumferential fiber shortening (circumferences/sec).

apical marker. The position of the aortic valve plane was established by translation of the aortic marker coordinates based on superimposition of the earliest postoperative fluoroscopic records on the preoperative left ventriculogram.

Analysis of segmental wall motion was based on construction of six perpendicular transverse radii from the long axis to each of the three anterior and three inferior markers. Figure 1 shows idealized spacing of three inferior and three anterior transverse radii and their designations R1 through R6, which were used for segment identification in this study. The percent shortening of individual radii (S) is the total shortening between end-diastole and end-systole divided by the end-diastolic chord length. Normal total segmental shortening is equal to, or exceeds, 12 percent based on control and post-isoproterenol observations in cardiac transplant recipients at the time of postoperative angiography.

Velocity of circumferential fiber shortening (V_{CF}) was computed for each segment by measuring the mean rate of shortening of the transverse radius during the initial 167 msec of systole after the maximal volume frame and then normalizing it using the initial diastolic transverse radius. Global velocity of circumferential fiber shortening for the ventricle was calculated in a similar manner using the mean ventricular diameter, that is, using the averaged measurements from six radii and dividing by three. The fact that individual segments terminate inward motion at quite different times led us to use a shortened ejection period for the segmental V_{CF} calculation in order to minimize the effects of heterogeneous onset of segmental relaxation. In addition, the use of a fixed time during the ejection phase prevents variations in ejection time secondary to changes in heart rate from directly affecting the V_{CF} computation. Normal values for segmental V_{CF} are 0.35 circumference/sec or greater.

Early systolic shortening (S_e) measures the percent shortening of each transverse radial length in the 133 msec after the time of maximal volume. Normal segments have early shortening equal to or greater than 1 percent.

Statistical analysis: All values reported are the mean of measurements obtained from four to nine cardiac cycles recorded immediately before and 1.5 hours after intravenous digoxin administration. Control and post-digoxin measurements were compared using paired and unpaired *t* tests, where appropriate. The reproducibility of each of the measurements used in this study was established by pooling the standard deviations for each patient over a number of different cardiac systoles. The pooled standard deviations for measures of global left ventricular function are: V_{CF} 0.07 circumference/sec, end-diastolic volume 3.8 ml, end-systolic volume 2.5 ml and ejection fraction 0.02. The pooled standard deviations for measurements of segmental dynamics are: segmental V_{CF} 0.20 circumference/sec, segmental total shortening 3.4 percent and segmental early shortening 5.0 percent.

Results

Overall left ventricular performance: The effects of acute administration of 1 mg of intravenous digoxin on overall left ventricular performance are summarized in Table II and have previously been reported.[6] V_{CF} increased by 16 percent ($P < 0.001$), ejection fraction by 6 percent ($P < 0.05$) and systolic pressure by 13 percent ($P < 0.01$). Heart rate declined from a mean of 69.7 to 62.8 beats/min ($P < 0.001$) accompanied by an 8.7 percent decrease in cardiac output.

Clinical correlates of abnormal segmental dynamics: Segmental dynamics were evaluated using three separate measurements: total shortening, early shortening and segmental V_{CF}. Table I lists the sites of segmental abnormality according to the following criteria: (1) Normal total shortening of 12 percent or more; (2) normal early shortening of 1 percent or more, and (3) normal segment V_{CF} of 0.35 or more.

Table I shows the clinical correlates of abnormal segmental dynamics—namely, electrocardiographic sites of prior infarction, distribution of coronary arterial lesions and location of preoperative segmental abnormalities based on myocardial marker measures and ventriculographic assessment of segmental dynamics. The site of prior infarction is based on the presence of pathologic Q waves in the electrocardiogram and the site of ventriculographic abnormalities is based on radiographic assessment of the right anterior oblique projection. The location of infarction by electrocardiographic criteria and ventriculographic abnormalities correlates well with the distribution of coronary vessels with lesions in excess of 80 percent luminal stenosis. The site of prior muscle damage generally correlates with abnormal segmental dynamics. Early shortening and segmental V_{CF} tend to be more sensitive than total shortening to subtle abnormalities of segmental dynamics. Thus, most abnormal segments defined by these criteria are in locations coincident with electrocardiographic and angiographic sites of prior infarction and are located in the distribution of severely stenotic coronary vessels.

Effects of intravenous digoxin on segmental ventricular performance: Table III summarizes the effects of intravenous digoxin on measurements of segmental performance. Total segmental shortening from end-diastole to end-systole increased 4.5 percent and early shortening increased 13.5 percent (both *P*

TABLE II

Effect of Intravenous Digoxin on Global Ventricular Performance in Nine Patients*

	V_{CF}	EF	EDV	CO	HR	BP	
						S	D
Control	0.67 ± 0.06	0.50 ± 0.03	135 ± 13	4.6 ± 0.4	69.7 ± 4	109 ± 5.6	63 ± 3.2
Digoxin	0.78 ± 0.06	0.53 ± 0.03	132 ± 12	4.2 ± 0.3	62.8 ± 5	123 ± 6.3	66 ± 3.3
P value	<0.001	<0.05	NS	<0.05	<0.001	<0.01	NS

* Mean of four to nine cardiac cycles per patient. All values given as mean ± standard error of the mean.
BP = blood pressure (mm Hg); CO = cardiac output (liters/min); D = diastolic; EDV = end-diastolic volume (ml); EF = ejection fraction; HR = heart rate (beats/min); *P* = probability; S = systolic; V_{CF} = velocity of circumferential fiber shortening (circumferences/sec).

TABLE III

Effect of Intravenous Digoxin on Segmental Performance in Nine Patients (no. of segments = 54)*

	Segmental Shortening (%)	Early Shortening (%)	Segmental V_{CF}
Control	19.9 ± 1.6	3.7 ± 0.5	0.63 ± 0.06
Digoxin	20.8 ± 1.8	4.2 ± 0.6	0.71 ± 0.06
P	<0.025	<0.025	<0.005

* Six segments in each of nine patients: mean of four to nine cardiac cycles per patient. All values given are mean ± standard error of the mean.

P = probability; V_{CF} = velocity of circumferential fiber shortening (circumferences/sec).

<0.025 by paired *t* test). Segmental V_{CF} increased 12.7 percent (P <0.005).

To assess baseline function of those segments that respond to digoxin as compared with those which do not, the results of all three indexes of segmental performance were used to categorize segments into normal, borderline and abnormal categories. Segments that have normal values for all three measurements of segmental performance were considered normal whereas segments having only two of the three measurements normal were considered borderline. Segments with more than one abnormal measurement were categorized as abnormal. Of the 54 segments available for analysis (six segments in each of nine patients), 34 had normal baseline function, 9 were considered borderline and 11 were classed as abnormal.

Table IV summarizes the relation between baseline function and response to intravenous digoxin for all three indexes and confirms that beneficial responses to digoxin occur more frequently in normal segments than in borderline or abnormal segments. Total shortening was maintained or improved in 91 percent of normal segments (31 of 34) but was maintained or improved in only 45 percent of abnormal segments (5 of 11). Similarly, using segmental V_{CF} as the criterion, 8 of 13 segments (62 percent) showing deterioration in segmental performance had abnormal or borderline baseline function. Qualitatively similar results were obtained for total and early shortening.

Illustrative responses of individual segments to digoxin: Figures 2 to 4 display examples of the responses of individual segments to intravenous digoxin. The single transverse radius having the poorest baseline systolic shortening was selected for illustration from each of the nine patients. Figure 2 shows the response of normal segments in two patients, both of whom maintained normal function after intravenous digoxin. The pre- and post-digoxin transverse radii are superimposed using the QRS complex as a fiducial marker. Heart rate declined after intravenous digoxin, accounting for the discontinuity in plotting of control data just before end-diastole. The small oscillations (averaging 1 mm excursion or less) were caused by random digitizing errors.

Figure 3 shows the response of segments having borderline baseline function and are segments with the lowest total shortening in three patients. The transverse radius shown in Figure 3C demonstrates early systolic lengthening of the transverse radius extending to the mid anterior wall segment. After digoxin, the length of the transverse radius diminished; however, the early systolic bulge (the early paradoxical motion shown by the arrow in Fig. 3) is still prominent. Severe left anterior descending coronary artery stenosis had been present in this patient, who had had coronary bypass surgery.

Figure 4 shows the response to digoxin of distinctly abnormal transverse radii from four patients. Shortening is either minimal (panels A and B) or frankly paradoxical (panels C and D). Both panels C and D show slightly more prominent paradoxical motion after digoxin, which is reflected in a decline in both total and early shortening computed from these transverse radii.

The tendency for heterogeneous segmental responses to digoxin is suggested by a plot of two segments from the same patient (Fig. 5). Inferior wall segment R3 with normal baseline function shows improvement in total shortening and V_{CF} after digoxin. In contrast, the paradoxically moving anterior wall segment (R4) in an area of prior infarction shows increased late systolic paradox after digoxin. Heterogeneous segmental responses of this type could be identified in three patients, and were generally present in

TABLE IV

Response of Individual Segments to Intravenous Digoxin (improved or maintained function versus deteriorated* function)

Segments Type	Segments no.	Velocity of Shortening	Total Shortening	Early Shortening
Normal	34			
Improved		29 (85%)	31 (91%)	28 (83%)
Deteriorated		5 (15%)	3 (9%)	6 (18%)
Borderline	9			
Improved		6 (67%)	6 (67%)	4 (44%)
Deteriorated		3 (33%)	3 (33%)	5 (56%)
Abnormal	11			
Improved		6 (55%)	5 (45%)	5 (45%)
Deteriorated		5 (45%)	6 (55%)	6 (55%)
P value		NS	<0.01	<0.02

* Deterioration is defined as a decline in a segmental index of more than 6 percent from the control value.
NS = not significant; *P* value = probability value obtained with chi square analysis.

those patients with the greatest disparity between normal and abnormal segmental motion.

Discussion

Response of diseased versus normal ventricular segments to digoxin: It is well established that digitalis exerts a positive inotropic effect when administered acutely to the nonfailing heart.[1-2,11] Our data demonstrate an acute augmentation of overall left ventricular performance 1.5 hours after intravenous digoxin and are in agreement with previously reported findings.[1-2,11] Although overall ventricular performance, as commonly measured by ejection phase indexes, does show improvement, it is of interest to know to what extent

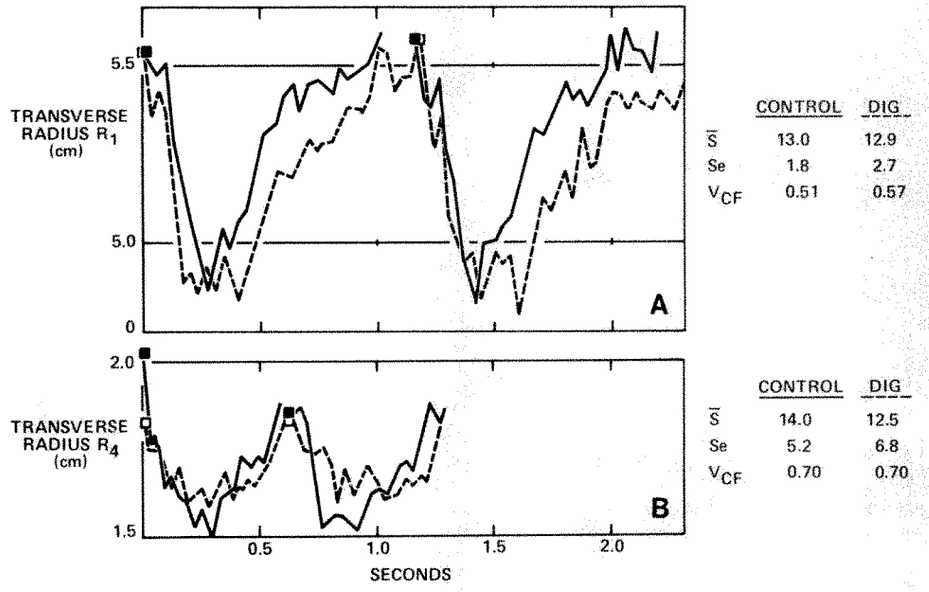


FIGURE 2. Transverse radii from two normal segments with superimposition of the control **(solid lines)** and intravenous digoxin (DIG) **(dashed line)** length-time plots. The **closed squares** indicate the end-diastolic frame. Little change in numeric values of total shortening ($\bar{S}$), early shortening (S_e) or segmental velocity (V_{CF}) is noted, and this finding is consistent with the virtual superimposition of the systolic portions of the graphs. Segmental data are shown from Cases 6 and 1 (**A** and **B**, respectively). DIG = digoxin.

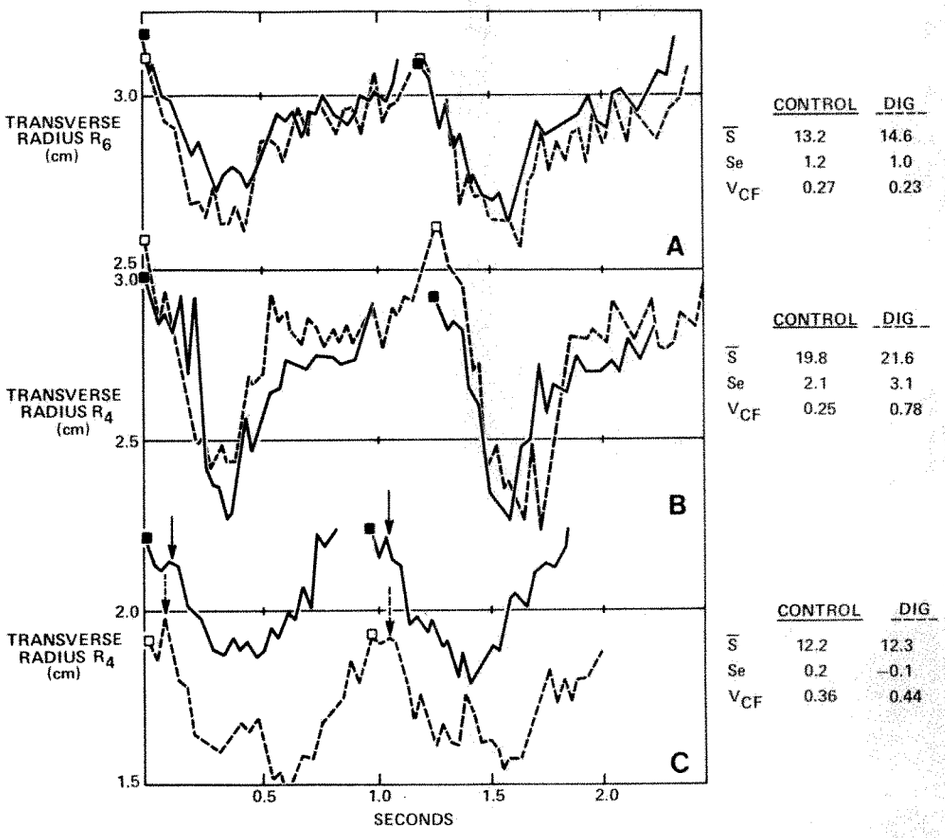
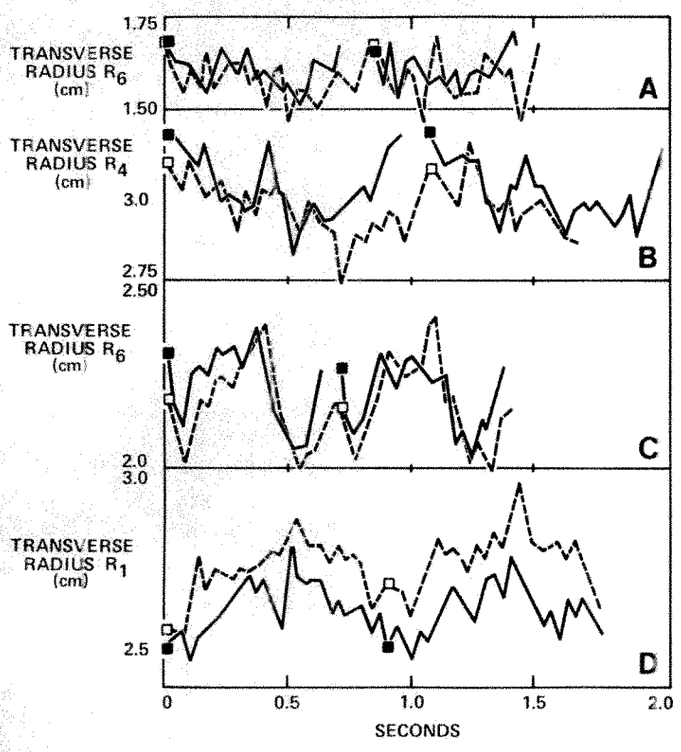
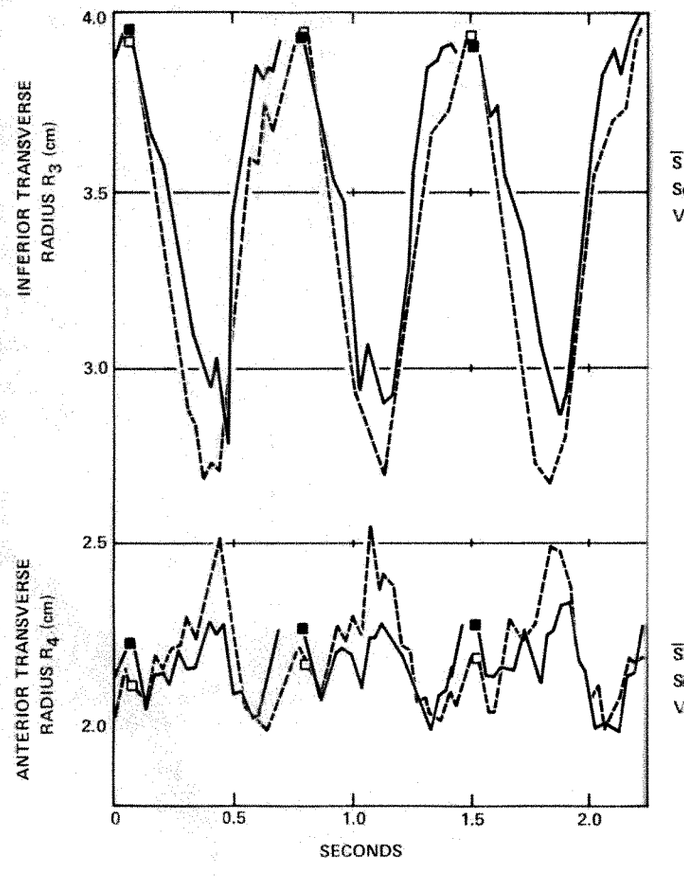


FIGURE 3. Length-time plots for transverse radii from three separate ventricles, each of which exhibited borderline baseline function. The **arrows** in **C** point out early systolic paradox, which is reflected in the abnormal early shortening measurement (S_e), whereas both total shortening ($\bar{S}$) and segmental velocity (V_{CF}) are within the normal range. The data shown are from Cases 7, 8 and 9 (**A, B** and **C,** respectively).



	CONTROL	DIG
$\bar{S}$	1.7	3.6
Se	3.3	4.0
V_{CF}	0.25	0.20
$\bar{S}$	5.0	4.5
Se	0.9	1.4
V_{CF}	0.07	0.15
$\bar{S}$	−2.3	−6.6
Se	4.0	2.4
V_{CF}	−0.02	−0.36
$\bar{S}$	−5.1	−5.2
Se	0.1	−1.0
V_{CF}	−0.19	−0.28

FIGURE 4. The response to digoxin (DIG) of four abnormal transverse radii. Baseline total shortening ($\bar{S}$), early shortening (S_e), and segmental velocity (V_{CF}) are abnormal in all cases. Plots **C** and **D** exhibit distinct paradox by the end of systole, which is slightly accentuated after intravenous administration of digoxin. The data shown are from Cases 2, 5, 4 and 3 (**A, B, C** and **D,** respectively).



	CONTROL	DIG
$\bar{S}$	27.3	30.8
Se	6.5	6.5
V_{CF}	0.78	1.05
$\bar{S}$	−1.3	−8.8
Se	4.4	2.5
V_{CF}	0.23	−0.15

FIGURE 5. The mid inferior transverse radius and mid anterior transverse radius from a single patient (Case 4) are plotted against time. The inferior wall (R_3) contracts normally under control conditions, whereas the anterior segment (R_4) has slight systolic paradox (negative total shortening $-\bar{S}$) and an abnormally low velocity (V_{CF} <0.35). After intravenous administration of digoxin (DIG), the normal segment (R_3) exhibits increased total shortening and velocity, whereas the segments showing abnormal baseline function (R_4) exhibit greatly accentuated end-systolic paradox.

damaged segments respond to digitalis as compared with normal segments. Although one can compare the effects of digitalis on the heart in normal patients with the responses in patients having cardiac disease, the approach we have taken is to examine the responses of normal and diseased segments within the same left ventricle. Surgically implanted markers were positioned in a geometric pattern that included both normal segments and segments that were partially or severely scarred by prior myocardial infarction. The small size of the myocardial markers and the use of a fluoroscopic recording technique that utilizes a synchronized electrocardiogram and digital processing techniques permitted high resolution analysis of regional wall dynamics before and after digoxin.

Two of the three indexes chosen for assessing segmental responses to intravenous digoxin are analogous to ejection phase indexes used for evaluating the intact ventricle (total systolic segmental shortening is an analog of the ejection fraction, and segmental V_{CF} is an analog of total ventricular V_{CF}). Early shortening was developed as an index to quantitate transient paradox during the initial portion of systole that was not detected by measurement of total segmental shortening or segmental V_{CF}. Figure 3 shows an example of an early systolic wall motion abnormality that did not result in abnormal total shortening. The criteria used to define normal segmental indexes are based on analysis of segmental motion in cardiac transplant recipients who had normal ventriculograms and were free of rejection at the time of study. In patients with coronary disease, segments from areas relatively unaffected by coronary lesions and surgical intervention exhibited similar values.

Reasons for deterioration of segmental performance after digoxin: Although it might be hoped that digoxin would exert beneficial inotropic effects most prominently in regions of abnormal wall function, the greatest augmentation of contractility occurred in segments that demonstrated normal baseline function. Deterioration of segmental performance occurred after digoxin in approximately 50 percent of segments with abnormal baseline function. This observation could be explained by increased afterload due to the small but significant increase in systolic blood pressure that resulted from digoxin administration and could contribute to segmental deterioration. An alternative possibility is that segments with impaired baseline function are less able to sustain the increased wall tension resulting from increased contractility of normal myocardial segments induced by digitalis. Hodges et al.[12] suggested that the failure of abnormal segments to respond to digoxin partially explained the lack of responsiveness to digitalis in patients after myocardial infarction.

Our data are consistent with those of a prior animal study reported by Banka et al.[13] in which acute ischemia was carried beyond the point of reversibility (more than 45 minutes after coronary occlusion). These investigators showed that digoxin had no effect on the segments exposed to prolonged ischemia, whereas normal nonischemic segments benefited from digoxin. However, it should be noted that abnormal baseline segmental function in our study was usually the result of prior scar formation rather than the result of ischemia because no patient had angina at the time of study.

Clinical implications: Our results suggest that, in patients with coronary artery disease who do not have congestive heart failure, segmental responses to digoxin are complex and variable, even though net augmentation in overall ventricular performance can be demonstrated.[6] They indicate that the response of individual segments to digoxin depends on the amount of viable nonischemic muscle in the ventricular wall.[14] Intraoperative ventricular biopsy techniques confirm that the degree of scarring and fibrosis within the myocardial wall correlates with segmental contractility assessed angiographically as well as with the presence of pathologic Q waves.[15] The spectrum of segmental responses to digoxin that we observed seems to be the result of the heterogeneous composition of myocardial wall segments. Our results suggest that, in ventricles with prior scarring, administration of digoxin results in greater heterogeneity and asyneresis of myocardial segment performance due to further deterioration of function in some segments, although global left ventricular function is improved.

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Effect of Isosorbide Dinitrate on Response to Submaximal and Maximal Exercise in Patients With Congestive Heart Failure

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Isosorbide dinitrate is an effective vasodilator that improves resting left ventricular performance in patients with congestive heart failure, but little is known of the effect of the drug on the response to exercise. Bicycle exercise to symptomatic maximum was performed by 18 patients with class II to IV congestive heart failure before and 90 minutes after administration of isosorbide dinitrate, 40 mg orally. Although resting pulmonary wedge pressure and systemic vascular resistance were significantly reduced after isosorbide dinitrate, exercise duration was not altered and maximal oxygen consumption was not significantly changed (13.6 ± 1.3 [SEM] standard error of the mean versus 13.8 ± 1.2 ml/kg per min). At peak exercise pulmonary wedge pressure of 37.1 ± 1.7 mm Hg, cardiac index of 4.19 ± 0.35 liters/min per m^2, and systemic vascular resistance of 14.7 ± 1.3 units were not significantly different after nitrate administration. However, at submaximal loads, pulmonary wedge pressure was reduced from 33.6 ± 1.7 to 27.9 ± 1.8 mm Hg ($P < 0.01$), and systemic resistance from 16.5 ± 1.5 to 13.7 ± 1.0 units ($P < 0.01$) after administration of isosorbide dinitrate. Thus, short-term administration of nitrates does not improve maximal exercise capacity or left ventricular performance at maximal exercise in patients with congestive heart failure, but it does appear to improve pump function at submaximal work loads and may therefore enable patients to perform limited exercise more comfortably.

Nitrates are effective vasodilators that improve resting left ventricular performance in patients with left ventricular failure and are being widely used in the long-term management of chronic heart failure.[1–6] Although patients with congestive heart failure are symptomatic especially during exertion, the effects of nitrates on exercise capacity and exercise hemodynamics have not been well defined in such patients.

Patients with congestive heart failure are limited in their ability to exercise because of dyspnea from elevated pulmonary capillary pressure or because of fatigue from inadequate cardiac output.[7] Because nitrates consistently decrease pulmonary capillary pressure and usually increase reduced cardiac output at rest, these same effects, if maintained during exertion, could increase exercise capacity.[1] We[8] have recently observed that long-term nitrate therapy increases treadmill exercise time in patients with congestive cardiomyopathy. It has also recently been reported[9] that acute nitrate administration modestly improves exercise capacity and hemodynamics in patients with valve insufficiency. However, the uniquely beneficial effect of vasodilator therapy in patients with regurgitant valve lesions might have contributed to this response.[10,11] The present study was therefore carried out to assess the immediate effects of isosorbide dinitrate on exercise capacity and hemodynamics in patients with left ventricular failure due to myocardial disease.

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Methods

Patients: Studies were performed in 18 patients with class II to IV congestive heart failure (according to New York Heart Association criteria[12]). Their age averaged 59 ± 1.4 (mean ± standard error of the mean) years (range 46 to 70 years). The cause of congestive heart failure was ischemic cardiomyopathy in 13 patients and primary cardiomyopathy in 5.

Ischemic cardiomyopathy was diagnosed on the basis of a history of documented acute myocardial infarction, a history of typical angina pectoris in the past or arteriographic evidence of obstructive coronary artery disease. Primary cardiomyopathy was diagnosed when no other cause for congestive heart failure was apparent. Patients were selected for study because they were limited by symptoms of shortness of breath or fatigue on exertion. Patients with angina were excluded as well as those with primary lung disease, acute myocardial infarction within the previous 4 months or intermittent claudication. All patients had been receiving maintenance doses of digitalis and diuretic drugs before study. Six patients had previously been taking some form of vasodilator therapy for congestive heart failure.

On the day of study, after written informed consent had been obtained, the patients were taken to an exercise laboratory located in an air-conditioned room with constantly maintained temperature and humidity. All patients were studied in the postabsorptive state at least 2 hours after ingestion of any food. Previous vasodilator therapy was stopped 48 hours before study, and diuretic drugs were withheld for at least 12 hours before study. Maintenance digitalis doses were continued.

Hemodynamic measurements: Swan-Ganz catheterization was performed percutaneously by way of an antecubital or femoral vein and the catheter was advanced under pressure monitoring to the pulmonary artery for monitoring of pulmonary arterial pressures. The pressure transducer was positioned at the intersection of a line drawn transversely through the angle of Louis and the mid axillary line with the patient supine. This same transducer position was used with the patient in the sitting position. In any given patient the value for pulmonary wedge pressure was taken from that for either arterial diastolic or pulmonary arterial occluded pressure, and these pressures were not interchanged in the same patient. The heart rate and electrocardiogram were monitored from a standard V_5 lead, and blood pressure was measured with the cuff technique. Expired air was collected and passed in series through a Parkinson-Cowan dry gas meter, a Beckman LB2 carbon dioxide analyzer, and a Beckman OM14 oxygen analyzer, whose outputs were displayed on a Beckman RR2 recorder. Thus oxygen consumption and carbon dioxide production were monitored continuously on line. Cardiac output was measured using the carbon dioxide rebreathing method, which has previously been validated at rest and during exercise in normal subjects as well as in patients with congestive heart failure.[13,14] Details of this totally noninvasive, indirect Fick procedure have previously been described.[15]

Exercise protocol: Measurements were made during supine and sitting rest. Exercise was then performed on a Monark bicycle ergometer beginning at 150 kilopond-meters per minute (kpm/min) and increasing the work load by 150 kpm/min every 4 minutes until the patient's symptomatic maximum was reached. Achievement of maximal aerobic exercise was verified by a significant increase in the respiratory exchange ratio, which correlates with the onset of lactate production.[16,17] All patients were limited by dyspnea or fatigue and no patient stopped because of angina, arrhythmia or electrocardiographic changes.

After completion of the control exercise test, and when supine heart rate, blood pressure and pulmonary wedge pressure had recovered to baseline levels, patients were given isosorbide dinitrate, 40 mg, by mouth. Supine, sitting and exercise measurements were repeated 90 minutes later. This time period was chosen on the basis of our previous findings[18] that the peak hemodynamic effects of oral isosorbide dinitrate occur within 1 hour and persist unchanged for 2 hours in patients with congestive heart failure. Exercise hemodynamic measurements were made during the final minute of each work load.

Mean arterial pressure was calculated as diastolic arterial pressure plus one third the pulse pressure. Systemic vascular resistance was calculated as mean arterial pressure divided by cardiac output. Statistical analysis was performed employing Student's paired t-test.

TABLE I

Effects of Isosorbide Dinitrate on Supine Resting Hemodynamics in Patients with Congestive Heart Failure*

	Control	Isosorbide Dinitrate	P
Number of patients	18	18	
Heart rate (beats/min)	82.0 ± 2.6	78.5 ± 2.2	NS
Mean arterial pressure (mm Hg)	86.7 ± 2.6	80.3 ± 3.0)	<0.01
Pulmonary wedge pressure (mm Hg)	24.3 ± 1.8	15.7 ± 1.6	<0.001
Cardiac index (liters/min per m^2)	2.10 ± 0.17	2.16 ± 0.11	NS
Systemic vascular resistance (units)	24.3 ± 1.6	21.1 ± 1.4	<0.05

* Values shown are group means ± standard error of the means. NS = not significant; P = probability.

Results

Resting hemodynamics: Changes in supine resting hemodynamics after isosorbide dinitrate are summarized in Table I. The decreases in pulmonary wedge pressure and mean arterial blood pressure, along with a slight increase in cardiac index, were those usually observed after nitrate administration in congestive heart failure. Systemic vascular resistance was significantly reduced in this group of patients, thus indicating an arterial dilating effect of the nitrates.

Effects of isosorbide dinitrate on maximal exercise capacity and hemodynamics at maximal exercise: Because the peak work load achieved varied among patients, the values reported in Table II represent those recorded at the individual maximum attained by any given patient. Only two patients exercised to different loads (both higher) after isosorbide dinitrate, but their maximal oxygen consumption at these higher loads was not increased after treatment. Cardiac index was not measurable in one patient who could not exercise long enough at maximum to permit satisfactory measurement of cardiac output, and blood pressure was inaudible during exercise in one patient because of previous bilateral brachial arterial obstructions. Exercise capacity, expressed as either duration of exercise or maximal oxygen consumption achieved, was not significantly altered by isosorbide dinitrate. The drug

also had no significant effect on cardiac index, heart rate, pulmonary wedge pressure or mean arterial pressure at maximal exercise.

When exercise capacity was analyzed in groups of patients according to clinical class of symptoms or etiology of heart failure, there were no significant differences observed after nitrate administration in any subgroup. In four patients with class II heart failure, maximal oxygen consumption achieved averaged 20.8 ± 2.5 ml/kg per min before and 19.6 ± 1.6 after isosorbide dinitrate. In 10 patients with class III heart failure the values were 12.6 ± 1.1 ml/kg per min before and 13.3 ± 1.2 after nitrate administration, and in patients with class IV heart failure values were 9.2 ± 1.2 ml/kg per min before and 9.0 ± 1.3 after nitrate administration. In the 13 patients with ischemic disease the maximal oxygen consumption achieved averaged 13.0 ± 1.6 ml/kg per min before isosorbide dinitrate and 13.5 ± 1.5 after. The five patients with primary cardiomyopathy averaged 15.3 ± 1.9 ml/kg per min before and 14.5 ± 1.9 after drug administration.

Effects of isosorbide dinitrate during submaximal exercise: Although isosorbide dinitrate failed to alter hemodynamic variables at maximal exercise, it had significant effects during submaximal work. Oxygen consumption was unchanged at any given exercise load after nitrate administration (Fig. 1). Because 16 of the 18 patients were able to perform more than the first exercise load, the data for these 16 patients were analyzed at their individual maximal and submaximal load levels. Submaximal values were taken at the next to highest work load achieved. Heart rate and cardiac index were not significantly different any time after isosorbide dinitrate, whereas mean arterial pressure was significantly reduced at sitting rest, but not during exercise after nitrate administration (Fig. 2). Pulmonary wedge pressure after administration of isosorbide dinitrate was reduced at sitting rest from 22.8 ± 2.5 to 14.2 ± 1.7 mm Hg ($P < 0.001$) as well as during submaximal exercise (33.6 ± 1.7 versus 27.9 ± 1.8 mm Hg, $P < 0.01$), but at maximal exercise the difference was also not significant in this subgroup of patients (Fig. 3). Although the values for blood pressure and cardiac index were not statistically significantly different after nitrate administration, the former tended to be lower and the latter, higher, so that there was a significant reduction in systemic vascular resistance at sitting rest (33.8 ± 2.6 versus 30.1 ± 2.4 units, $P < 0.02$) and during submaximal exercise (16.5 ± 1.5 versus 13.7 ± 1.0 units, $P < 0.01$) in this subgroup; however, the difference in systemic vascular resistance at maximal exercise was not significant after administration of isosorbide dinitrate (Fig. 3).

Orthostatic symptoms were observed in two patients (Cases 10 and 16) after nitrate administration. Both patients experienced lightheadedness in the sitting position, but the symptoms were transient and exercise was completed without difficulty. One patient was subsequently given intravenous fluids.

Role of reduced systemic vascular resistance at rest: The lack of significant effects of nitrates at peak exercise levels might be due to the fact that nitrates are thought to be predominant venodilators and to have less effect on arteriolar resistance. We therefore analyzed separately the data for patients who demonstrated a reduction in systemic vascular resistance at supine rest.

TABLE II

Effects of Isosorbide Dinitrate on Maximal Exercise Capacity and Hemodynamics at Maximal Exercise in Patients With Congestive Heart Failure

Case No.	Total Duration of Exercise (min)		Oxygen Consumption (ml/kg per min)		Heart Rate (beats/min)		Mean Arterial Pressure (mm Hg)		Pulmonary Wedge Pressure (mm Hg)		Cardiac Index (liters/min per m^2)		Systemic Vascular Resistance (units)	
	C	IS	C	IS	C	IS	C	IS	C	IS	C	IS	C	IS
1	19.4	20.0	24.8	24.4	149	138	106	93	35	18	4.83	5.14	11	9
2	14.8	14.0	23.9	17.6	125	125	99	97	50	35	6.09	6.06	9	9
3	7.0	6.8	9.4	14.7	127	113	87	92	31	32	....	....	...	...
4	4.0	4.0	8.6	8.2	134	150	129	130	46	44	3.03	2.66	24	27
5	9.8	10.5	13.7	17.5	158	167	...	...	36	40	4.77	5.15	...	...
6	7.2	7.2	13.0	11.4	100	111	75	71	38	40	2.87	2.99	15	14
7	6.5	7.0	12.6	12.9	135	125	108	107	49	40	4.74	5.08	11	11
8	7.5	7.2	17.7	15.4	136	136	92	87	37	40	2.94	3.15	18	16
9	4.0	6.0	7.2	7.9	108	108	97	98	35	37	3.02	3.83	16	13
10	6.1	6.7	10.9	13.3	130	136	105	103	35	29	3.01	4.31	21	14
11	19.5	18.7	20.8	18.8	195	192	120	118	30	27	7.25	5.41	8	10
12	7.5	7.3	8.7	8.8	107	103	85	85	36	32	3.24	3.55	14	13
13	9.7	9.5	14.4	18.9	126	128	104	100	28	30	6.50	8.32	9	6
14	7.8	8.0	11.5	11.2	122	122	91	106	32	31	3.97	4.29	12	13
15	9.6	8.8	12.6	11.6	130	118	105	103	46	39	3.48	3.34	14	14
16	11.9	10.8	18.8	19.6	125	112	94	96	25	20	5.44	5.52	10	10
17	4.0	4.9	9.5	7.6	134	146	105	102	38	48	3.05	3.28	20	18
18	1.5	1.8	7.5	7.7	104	102	115	106	40	48	2.93	3.52	23	17
Mean	8.8	8.8	13.6	13.8	130.3	129.6	101.0	99.6	37.1	35.0	4.19	4.45	14.7	13.4
SEM	1.2	1.1	1.3	1.2	5.2	5.5	3.2	3.2	1.7	2.0	0.35	0.35	1.3	1.2
P	NS		NS		NS		NS		NS		NS		NS	

C = control; IS = isosorbide dinitrate; NS = not significant; *P* = probability; SEM = standard error of the mean.

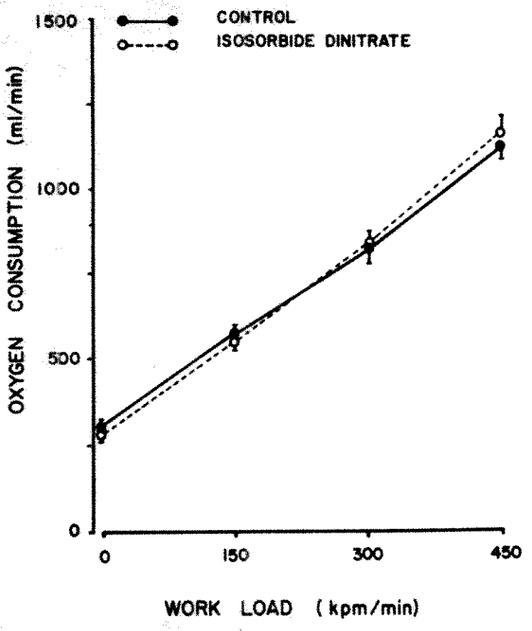


FIGURE 1. Effect of isosorbide dinitrate on oxygen consumption during exercise in patients with congestive heart failure. Mean values and standard error of the mean are plotted. No. of patients = 18 at 0 and 150 kilopond-meters per minute (kpm/min), 16 at 300 kpm/min and 7 at 450 kpm/min.

In this subgroup of 13 "good responders" the systemic vascular resistance decreased by 6.5 ± 1.0 units (P <0.001). At maximal exercise after nitrate administration, cardiac index in this group was increased insignificantly by 0.24 ± 0.24 liters/min per m^2, and pulmonary wedge pressure was reduced insignificantly by 1.3 ± 1.9 mm Hg. Exercise duration was insignificantly changed by 0.2 ± 0.2 minute and maximal oxygen consumption achieved was also insignificantly changed by 0.1 ± 0.8 ml/kg per min.

It is unlikely that these above results were influenced by patients not achieving aerobic exercise limits on both tests. That aerobic limits were achieved is suggested by the observation that the respiratory exchange ratio increased by 0.15 ± 0.03 (P <0.001) during the first exercise test and by 0.16 ± 0.03 (P <0.001) on the second test after nitrate administration.

Discussion

Our patients with congestive heart failure were significantly limited in their ability to exercise and could achieve a maximal oxygen consumption of only about 14 ml/kg per min. This result is similar to that reported by other investigators,[19] who found that patients with symptomatic heart failure could perform treadmill exercise usually only to oxygen consumption levels below 16 ml/kg per min. The cause of exercise limitation was probably related to the increase in pulmonary wedge pressure above 35 mm Hg and the failure of cardiac index to increase much above 4 liters/min per m^2. In normal subjects or patients with ischemic heart disease but without congestive heart failure, pulmonary wedge pressure increases slightly but usually does not exceed 20 mm Hg during upright bicycle exercise, whereas cardiac index may reach 7 liters/min per m^2 or more.[20,21] Because nitrates consistently decrease pulmonary wedge pressure and raise low cardiac output in patients with left ventricular failure, it was reasonable to postulate a beneficial effect of nitrates in our patients whose baseline cardiac index averaged just over 2 liters/min per m^2 with an average pulmonary wedge pressure of 24 mm Hg. Although the expected improvement in resting hemodynamics occurred in our patients after administration of isosorbide dinitrate, the hemodynamic effects were not apparent at high work levels, and maximal exercise capacity was not increased. Of course, in those patients in whom the value for pulmonary arterial diastolic pressure was used to determine pulmonary wedge pressure, we have assumed that this remains equal to pulmonary wedge pressure during exercise as well as at rest. Little is known about this relation during exercise and rapid heart rates, but the values we observed were similar to those reported for

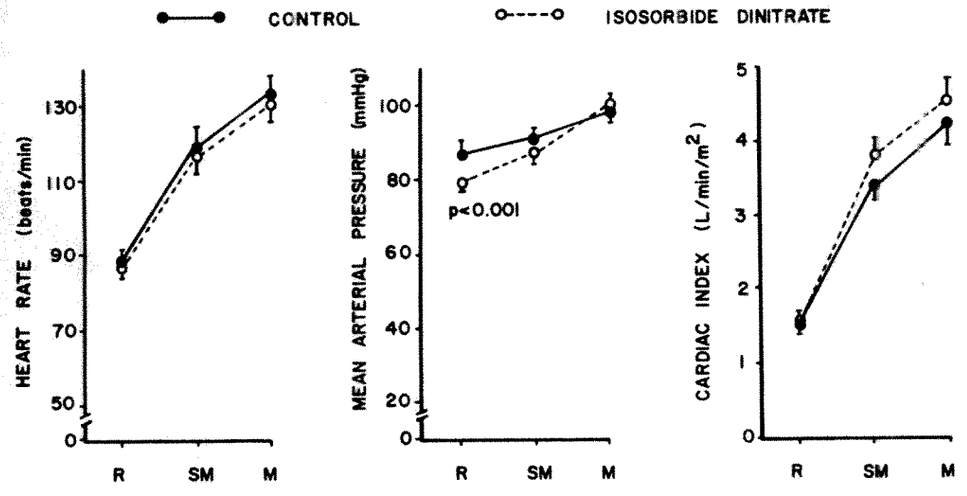


FIGURE 2. Effect of isosorbide dinitrate on heart rate, blood pressure, and cardiac index during exercise in 16 patients with congestive heart failure. Mean values ± standard error of the mean are plotted. L = liters; M = maximal exercise; p = probability; R = sitting rest; SM = submaximal exercise (next to highest work load).

left ventricular end-diastolic pressure during exercise in patients with heart disease.[21]

Mechanism of lack of effect of nitrates on maximal exercise capacity: The lack of acute effects of nitrates on exercise capacity in the present study could be due to several mechanisms. Although it is presumed that left ventricular outflow resistance decreases during exercise as the result of arteriolar dilation in exercising skeletal muscle, which is more pronounced at high exercise levels,[7] vasodilators may not augment this exercise-induced arteriolar dilation at high exercise loads. Our results are consistent with this hypothesis in that systemic vascular resistance was reduced at submaximal work loads, but not at maximal exercise after nitrate administration. Another possible explanation for our results is that the nitrates, which are predominant venodilators, had little arterial dilating effect. This seems unlikely because our group as a whole experienced a significant reduction in supine resting systemic vascular resistance after administration of isosorbide dinitrate, and separate analysis of the "good responders" in terms of decreased systemic vascular resistance, also failed to show any significant effect of nitrates at maximal exercise. Furthermore, when an arteriolar dilator such as hydralazine is added to the nitrate, our preliminary experience suggests that peak exercise capacity and hemodynamics are still not altered acutely.[22] It is also possible that patients with heart failure do not respond normally to vasodilator drugs because their responses to other vasodilator stimuli are impaired.[23] Our results could also have been influenced by a failure of patients to exercise to the same limit on each test, but this seems unlikely because the ventilatory exchange ratio rose significantly during both tests indicating attainment of aerobic limits.[16,17]

Finally, a control group of patients given placebo rather than isosorbide dinitrate might have strengthened the study design by including the effects of a second exercise test without active interventions. This was not done because in our preliminary experience a similar group of patients performing the same test before and after placebo failed to show any significant differences in exercise capacity or hemodynamics.[22] One might expect a second test to result in better exercise performance as the patient becomes more familiar and secure with the procedure, but we observed no differences in the present study and therefore believe that the lack of a placebo group does not significantly affect interpretation of our results.

Significance of improved hemodynamics at submaximal work loads: Although maximal exercise was not altered by nitrates in the present study, significant hemodynamic effects of isosorbide dinitrate were observed at submaximal work loads. Systemic vascular resistance was lower while cardiac index was maintained at a reduced left ventricular filling pressure (pulmonary wedge pressure), indicating an improvement in left ventricular performance. These effects may be more important than those at maximal exercise because patients with congestive heart failure rarely exercise at maximal levels. However, vasodilation may

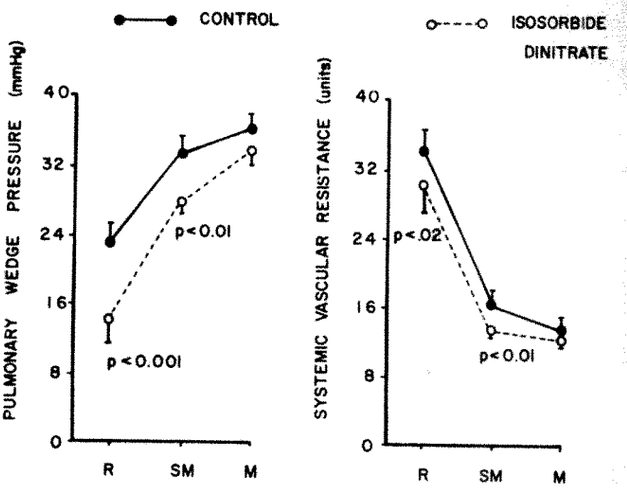


FIGURE 3. Effect of isosorbide dinitrate on pulmonary wedge pressure and systemic vascular resistance during exercise in 16 patients with congestive heart failure. Mean values ± standard error of the mean are plotted. M = maximal exercise; p = probability; R = sitting rest; SM = submaximal exercise (next to highest work load).

enable them to exercise at lower levels with fewer symptoms. In our study the duration of submaximal exercise was brief and the patients were unable to communicate well with the mouthpiece in place so that we could not accurately assess symptoms during these smaller work loads. However, clinical experience with nitrates and other vasodilators is consistent with symptomatic improvement during limited exercise because various authors[3–6] have reported an improvement in classification of symptoms by the New York Heart Association criteria, which are based on tolerance for exertion during vasodilator therapy.

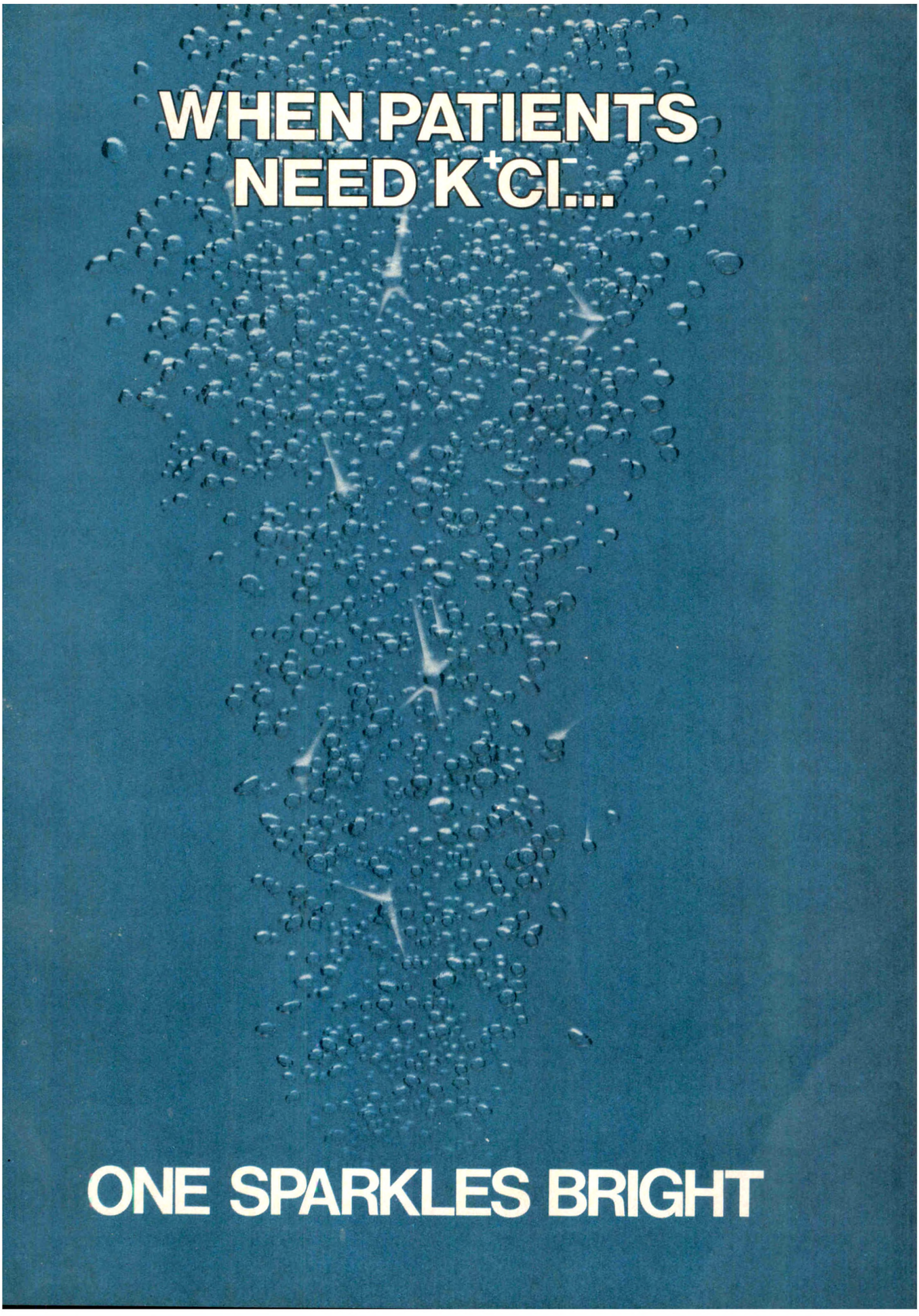
Clinical implications: Our results must be interpreted very cautiously because this study was intended only to observe the immediate effects of the first dose of isosorbide dinitrate. Although this vasodilator under these conditions exerted no significant effects on maximal exercise capacity or hemodynamics at peak exercise, preliminary experiences in small numbers of patients suggest that nitrates and other vasodilators administered for long periods can improve maximal exercise capacity.[3–6,8] The beneficial effects observed at lower work loads after single dose nitrate administration may be important in improving exertional symptoms in patients with congestive heart failure. Further studies of vasodilators are needed to assess the efficacy of these agents in chronic congestive heart failure. The present study suggests that exercise testing should be a vital part of all such studies.

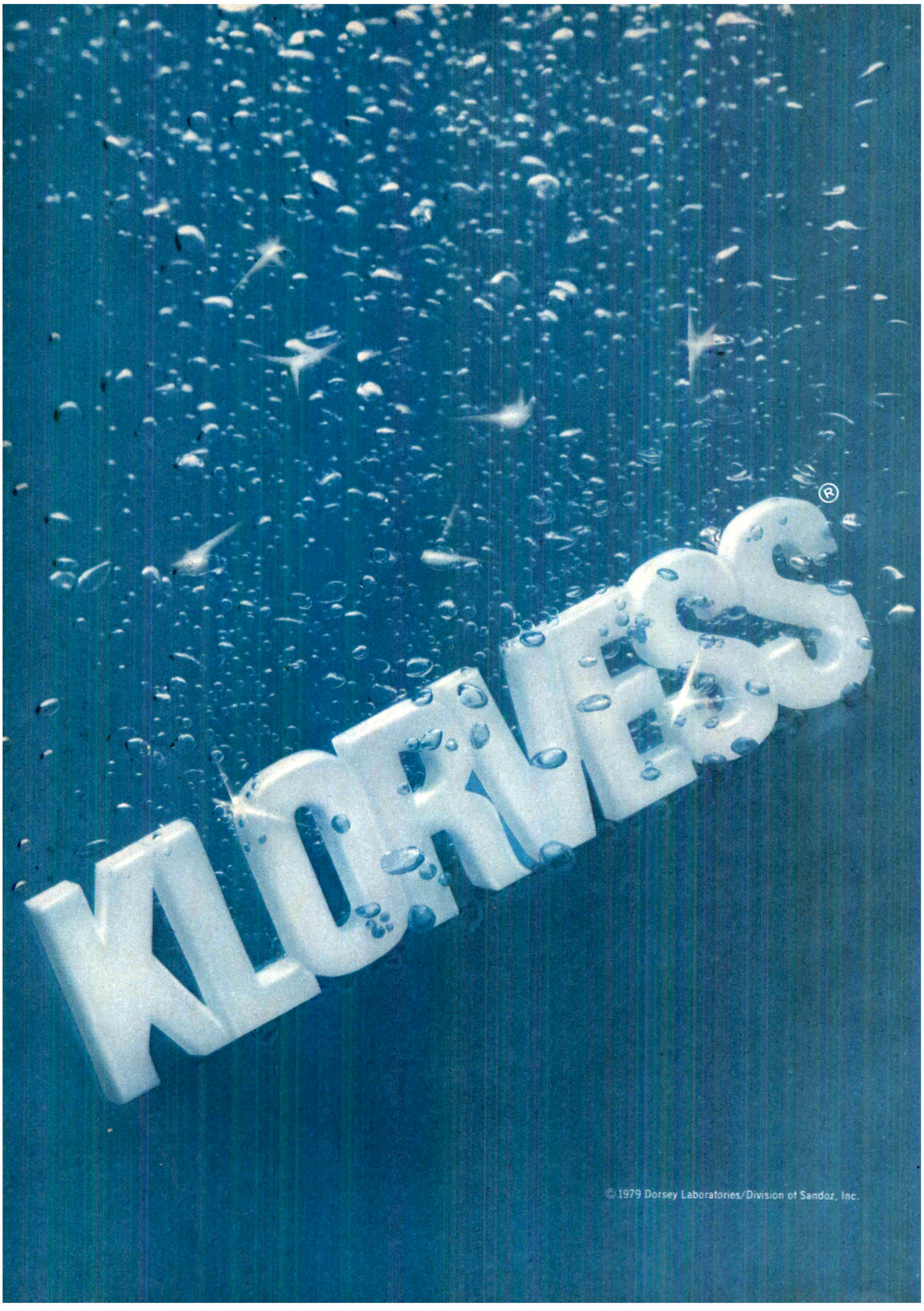
Acknowledgment

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Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

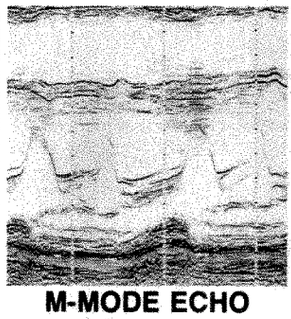
OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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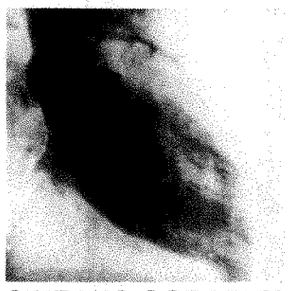
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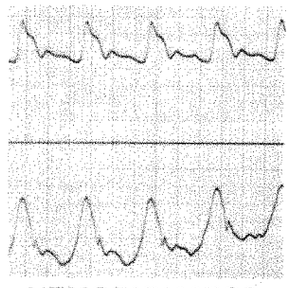
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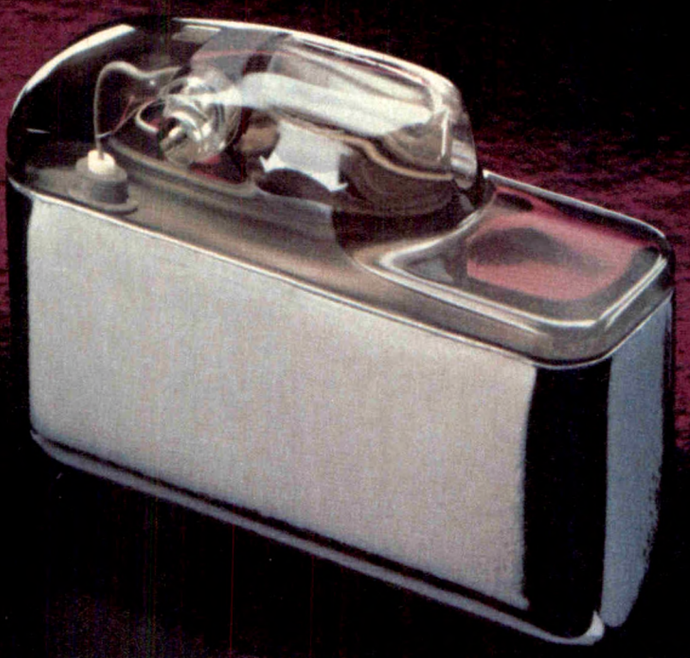
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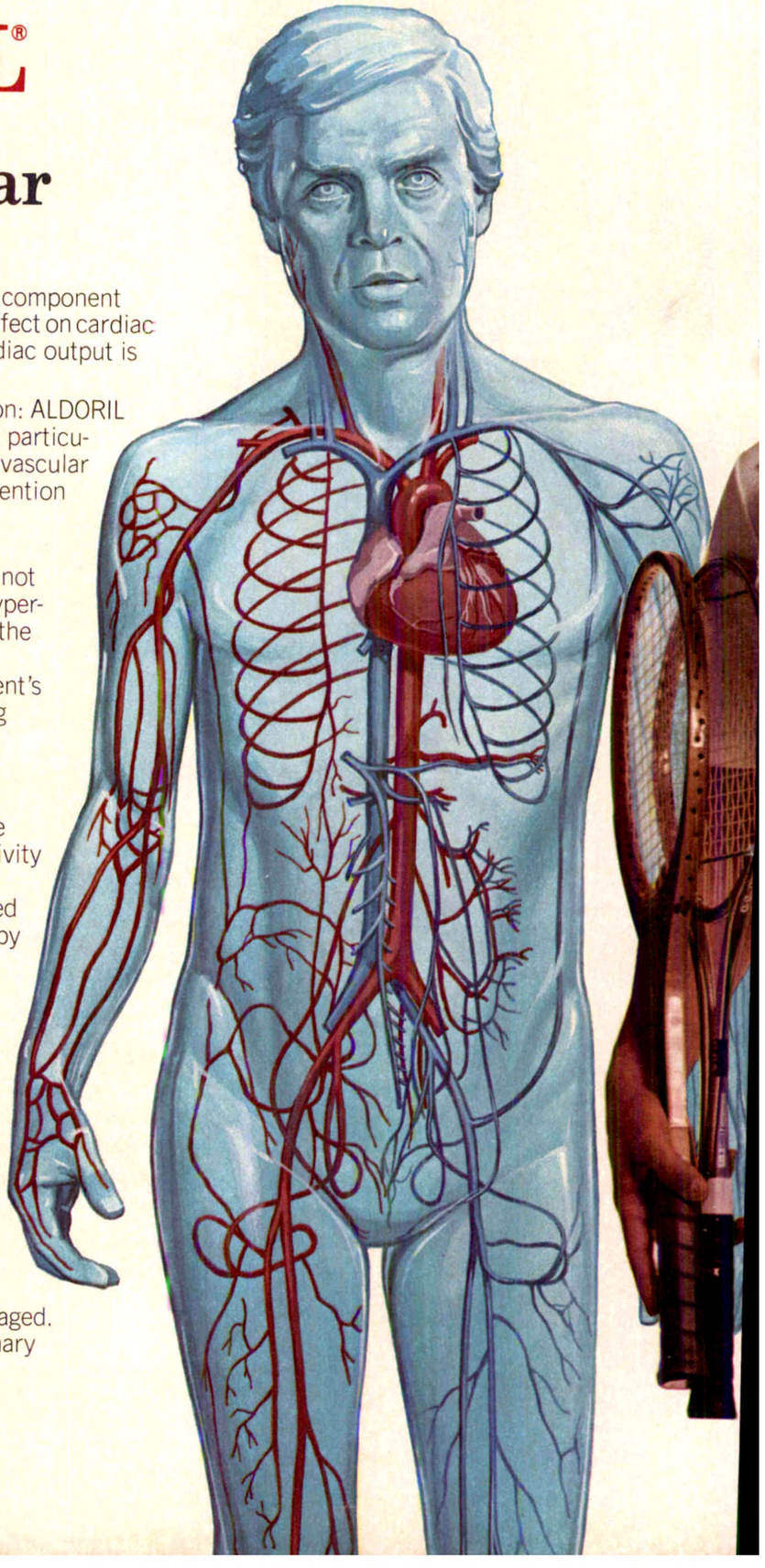
ALDORIL®
from the cardiovascular viewpoint

- ☐ A favorable cardiac profile: neither component of ALDORIL usually has any direct effect on cardiac function—in long-term therapy cardiac output is usually maintained.
- ☐ Control of sodium and fluid retention: ALDORIL often helps control fluid imbalance, particularly in those cases of hypertensive vascular disease where sodium and water retention is a problem.

As a fixed combination, ALDORIL is not indicated for initial therapy since hypertension requires therapy titrated to the individual patient. If an available strength of ALDORIL meets the patient's titrated needs, the combination drug may be more convenient in patient management. Therapy should be reevaluated as necessary.

ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.



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active hypertensives points of view



ALDORIL®
from the practical viewpoint

- ☐ Highly effective complementary agents: HydroDIURIL® (Hydrochlorothiazide, MSD), and ALDOMET® (Methyldopa, MSD), two well-accepted antihypertensives which usually maintain blood pressure control throughout the day.
- ☐ Greater dosage convenience (with a single tablet): a b.i.d. regimen is possible for many patients.
- ☐ Effect on daily activities usually minimal: there is less frequent symptomatic postural hypotension with ALDORIL than with many other antihypertensive agents. Exercise hypotension and diurnal blood pressure variations rarely occur.

ALDORIL®

containing methyldopa and hydrochlorothiazide

TABLETS
ALDORIL® D50
containing 500 mg ALDOMET® (Methyldopa, MSD) and 50 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
ALDORIL® D30
containing 500 mg ALDOMET® (Methyldopa, MSD) and 30 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
ALDORIL®-25 containing 250 mg ALDOMET® (Methyldopa, MSD) and 25 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
ALDORIL®-15 containing 250 mg ALDOMET® (Methyldopa, MSD) and 15 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

For a brief summary of prescribing information, please see following page.

MSD
MERCK SHARP & DOHME

Antihypertensive TABLETS
ALDORIL® D50
methyldopa 500 mg and hydrochlorothiazide 50 mg

Antihypertensive TABLETS
ALDORIL® D30
methyldopa 500 mg and hydrochlorothiazide 30 mg

Antihypertensive TABLETS
ALDORIL®-25
methyldopa 250 mg and hydrochlorothiazide 25 mg

Antihypertensive TABLETS
ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without mild edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

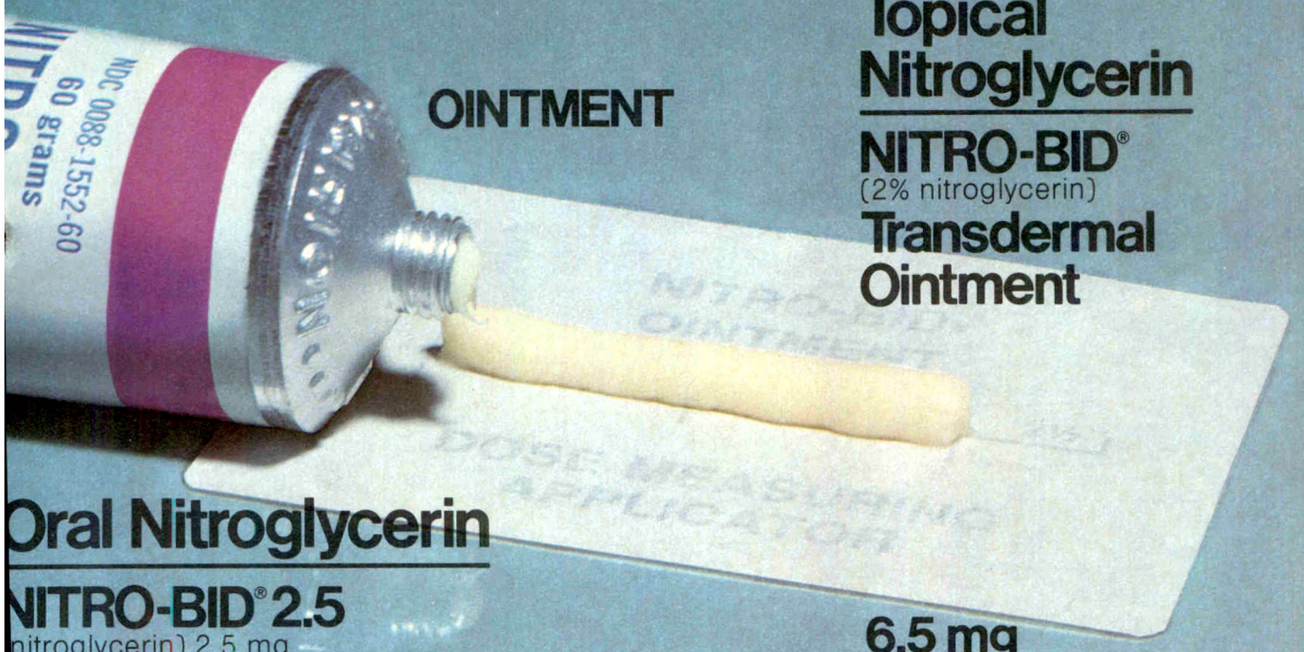
Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL® D30, containing 500 mg methyldopa and 30 mg hydrochlorothiazide, bottles of 100; Tablets ALDORIL® D50, containing 500 mg methyldopa and 50 mg hydrochlorothiazide, bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486. J8AR09-023J

MSD
MERCK SHARP & DOHME

Nitroglycerin from Marion Laboratories: the prophylaxis your angina patients need, the dosage flexibility you want.



Topical Nitroglycerin

NITRO-BID®
(2% nitroglycerin)
Transdermal Ointment

Oral Nitroglycerin

NITRO-BID® 2.5
nitroglycerin) 2.5 mg
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NITRO-BID® 6.5
nitroglycerin) 6.5 mg
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nitroglycerin) 9 mg
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6.5 mg



2.5 mg



9 mg



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PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MO 64137

dications
ased on a review of this drug and a related drug by the National Academy Sciences—National Research Council and/or other information, FDA has assified the indications as follows:

"Possibly" effective. When taken by the oral route, NITRO-BID Capsules are indicated for the management, prophylaxis or treatment of anginal attacks.

"Possibly" effective. When applied topically, NITRO-BID Ointment is indicated for the prevention and treatment of angina pectoris attacks especially at night.

nal classification of the less-than-effective indications requires further aluation.

ntraindications
tients with marked anemia, increased intraocular pressure, increased racranial pressure, glaucoma, hypotension, and idiosyncrasy to this drug.

Warnings
NITRO-BID is not intended to abort the acute anginal episode. NITRO-BID Capsules must be taken ORALLY, not sublingually. In terminating NITRO-BID Ointment treatment, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions.

Precautions
A headache is a definite sign of overdosage and, therefore, dosage should be reduced. Occasionally, elderly patients may have no untoward symptoms while recumbent, but may develop postural hypotension with faintness upon suddenly arising.

Adverse Reactions
With use of nitrates, transient headache, postural hypotension, flushing, tachycardia and dizziness may occur.

Consult full product disclosure before prescribing.


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There's only one disposable diaphragm dome that is designed and manufactured specifically for the Gould Statham P23 transducer.

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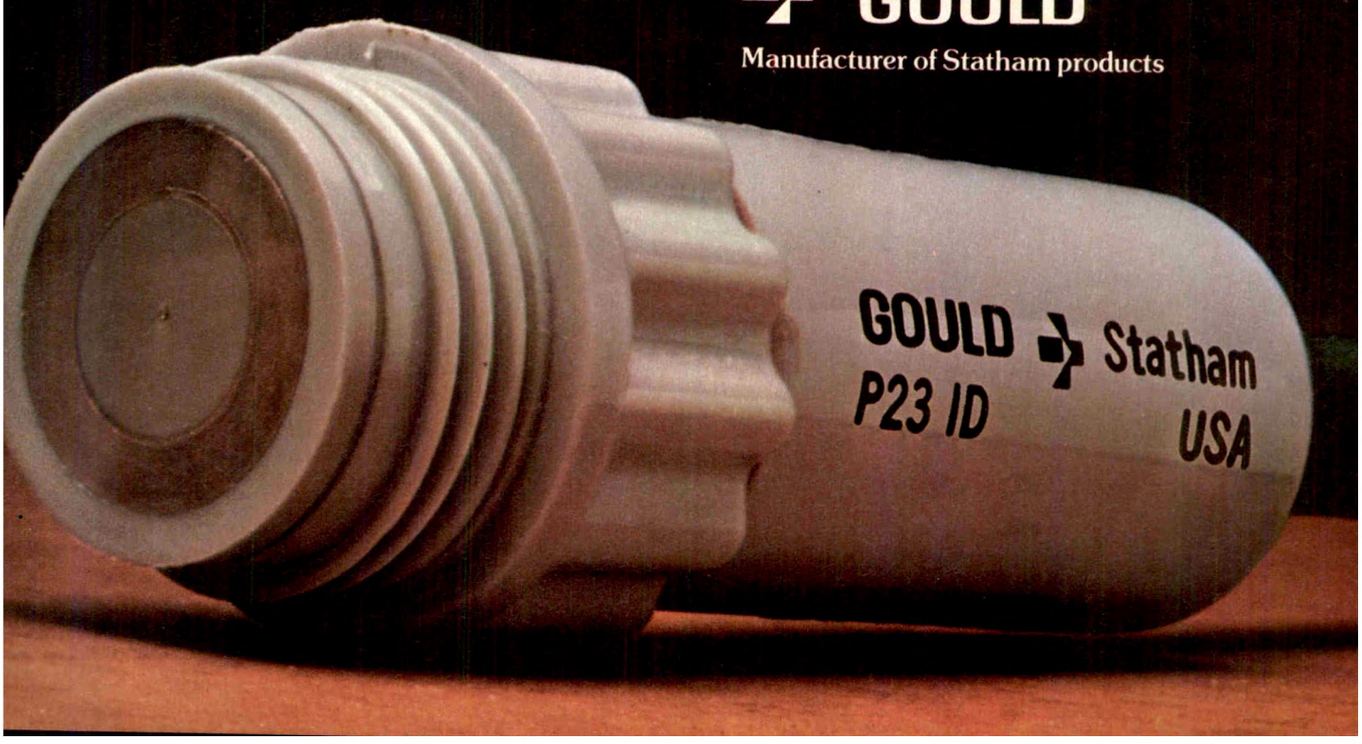
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Controlled Release In Nature



Controlled Release In Potassium Therapy

KAON-CL TABS®

(potassium chloride) Controlled Release Tablets

Helps encourage adherence to prescribed dosage schedules

When patient compliance with liquids or effervescent potassium is a problem, consider the convenience of the controlled release tablet from Warren-Teed. Just 2 KAON-Cl TABS t.i.d. equal 40 mEq potassium chloride.

minimizes the possibility of high localized concentrations of potassium in the GI tract

The reported frequency of GI lesions with wax-matrix tablets is less than 1 per 100,000 patient years. There have been only two equivocal cases of GI bleeding reported with KAON-Cl TABS to date and no reports of small bowel stenosis or ulceration. However, clinical experience is insufficient at this time to indicate the incidence is other than the stated numerical ratio.

BRIEF SUMMARY
KAON-Cl TABS® (potassium chloride)
Controlled Release Tablets

Description: Kaon-Cl Tabs is a sugar coated (not enteric-coated) tablet containing 500 mg potassium chloride (equivalent to 6.7 mEq potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: *Hyperkalemia*—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-Cl Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon-Cl Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

Caution: Federal law prohibits dispensing without prescription.

How Supplied: Bottles of 100, 250 and 1000.

WARREN-TEED LABORATORIES
DIVISION OF **ADRIA LABORATORIES INC.**
COLUMBUS, OHIO 43215

127827

A New
Inotropic Agent
for the Short-Term
Treatment of Low-Output
Cardiac Failure

Dobutrex®
Dobutamine HCl



Selectively Increases
Myocardial Contractility
with Consistent
Hemodynamic Improvements

See third page for brief summary of prescribing information.

Dobutrex®
Dobutamine HCl



Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051 Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/5 ml). The final volume administered should be determined by the fluid requirements of the patient. [08167]

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REVIEW

Strategy for Evaluation and Surgical Treatment of the Asymptomatic or Mildly Symptomatic Patient With Coronary Artery Disease

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Although there is no debate concerning the role of operation in severely symptomatic patients with coronary artery disease, uncertainty concerning the indications for coronary bypass operation in the asymptomatic or mildly symptomatic patient abounds. Preliminary results of the Veterans Administration Collaborative Study indicate that operation enhances survival only in patients with left main coronary artery disease. The debate this study engendered led to analyses questioning the validity of its conclusions. By utilization of nonrandomized data, it was argued that operation also increases survival in patients with significant narrowing of two or three coronary vessels. The survival data of the nonsurgically treated groups in such studies derived mainly from natural history data of populations studied 5 to 10 years ago and containing large numbers of severely symptomatic patients: The annual mortality rate in such populations has averaged about 7 and 11 percent in patients with two and three vessel disease, respectively. However, recent studies indicate that survival of asymptomatic or midly symptomatic patients with two or three vessel disease is considerably better: These patients have an average annual mortality rate of only about 2 percent. Thus, when survival data of surgically treated patients are compared with survival data of asymptomatic or mildly symptomatic patients not treated surgically, serious questions arise as to the wisdom of prophylactic operation in patients without left main coronary artery disease.

Because a compelling argument can be made for operating on all symptomatic patients with left main coronary artery disease it might be justified to perform coronary angiography in all symptomatic patients with coronary disease to rule out the possibility of significant left main arterial narrowing. Alternatively, electrocardiographic exercise stress testing may offer a reasonable alternative to determine which mildly symptomatic patients should undergo coronary angiography for detection of this disease. However, the profound economic implications of such screening studies must be considered before broad application of large scale screening is advocated.

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Uncertainty concerning the indications for coronary bypass surgery continues to perplex the practicing physician. It was hoped that the data derived from the prospective randomized studies from the Veterans Administration Collaborative Group and the Houston Veterans Administration Hospital on surgical versus medical treatment of patients with coronary artery disease[1–4] would resolve most questions as to the role of the coronary bypass operation. However, there will be no easy resolution. We have learned that the practical difficulties inherent in carrying out such large long-term prospective clinical trials raise ques-

tions that undermine the applicability of study results to formulating therapeutic strategies for other populations of patients treated by other physicians at other institutions. These virtually unavoidable limitations have plunged the medical community into a heated debate[5–11] that, for the present, cannot have a conclusive outcome.

Despite the lack of definitive data regarding indications for operation in patients with stable coronary artery disease, there is virtually no debate as to the efficacy of coronary bypass surgery in the amelioration of angina pectoris. Symptoms are improved in the large majority of patients,[3,7,8,12] and it has recently been shown with radionuclide cineangiography[13] that exercise-induced ischemic dysfunction is usually abolished. This latter finding indicates that alleviation of symptoms is most often due to an increase in myocardial flow, rather than to infarction of previously ischemic tissue. Therefore, if a patient can no longer enjoy a satisfactory life style despite comprehensive medical therapy for symptoms, and if angiographically determined coronary anatomy is conducive to a surgical approach, operation should be performed.

Patients With No or Mild Symptoms

The difficult choices regarding diagnostic and therapeutic strategies center on the patient with mild angina pectoris or the asymptomatic subject who on other grounds (such as an abnormal electrocardiographic response to exercise) is thought to have coronary artery disease. The diagnostic approach adopted is dependent on the physician's therapeutic strategy. A different diagnostic approach will be pursued if it is assumed that the coronary bypass operation is indicated for the purpose of improving survival in any patient with severe coronary stenoses than if operation is reserved for relief of severe symptoms. It is the purpose of this communication to review the studies that are most relevant to the role of surgery in the asymptomatic or mildly symptomatic patient and to incorporate information from these studies into a reasonable strategy for the evaluation and treatment of such patients.

Survival After Medical Versus Surgical Treatment

In formulating a therapeutic strategy for patients with no or mild symptoms, it is essential to know whether surgical intervention is likely to prolong life. At present, the only reported studies comparing medically versus surgically treated patients involve, by and large, relatively severely symptomatic patients. Although the applicability of such results to the asymptomatic or mildly symptomatic patient is highly questionable (a thesis that will be explored in more detail later), a brief review of these results is relevant. More detailed reviews of this particular subject are to be found in the recent articles of McIntosh and Garcia,[12] and of Hurst and colleagues.[7]

Randomized Studies

The most important study available to date is the Veterans Administration Collaborative Study,[1,2] in which patients were randomized prospectively into medically and surgically treated groups. In that study there has been, so far, no overall difference in long-term survival between patients undergoing coronary bypass surgery and those treated medically. However, when the patients with left main coronary arterial narrowing were analyzed separately, a statistically significant increase in survival was demonstrated in the patients operated on: 64 percent of the medically treated patients with left main coronary disease survived after 48 months of follow-up compared with 93 percent in the surgically treated subgroup.* If these results are generally applicable, it can be concluded that (1) patients with left main coronary artery disease should be operated on regardless of symptoms in order to prolong life, and (2) in patients without left main coronary artery disease, the indication for surgical treatment should be based on the severity of symptoms because survival is not enhanced.

Limitations of the Veterans Administration collaborative study: Although this collaborative study[1,2] is the most comprehensive study to date, the validity of its conclusions are limited for several reasons. First, the final study group consisted of 508 medically and 507 surgically treated patients. These subjects were selected from more than 5,500 subjects screened and more than 2,000 subjects who underwent arteriography. The exclusion from randomization of more than half the patients who had arteriography suggests that the selection process used was not based solely on the presence or absence of anatomic features conducive to operation. Part of the procedure for selecting appropriate subjects also required that patients have an abnormal electrocardiogram (either at rest or with exercise). Thus, 40 percent of the total randomized population had electrocardiographic evidence of prior myocardial infarction, a finding previously demonstrated to affect adversely long-term survival.[14] Moreover, 58 percent of the patients were in functional class III or IV before randomization, despite medical treatment. Thus, a majority of study patients, by today's standards, would qualify for operation on purely symptomatic grounds. On the basis of these considerations, it would be reasonable to question whether the study's selection criteria (with consequent elimination of more than 80 percent of those initially screened) allow generalization of the study's conclusions to other groups of patients with coronary artery disease.

Another important problem is the operative mortality rate of 5 percent, a figure excessively high by today's standards. This would unfavorably bias the results against the surgically treated patients. In addition, graft patency was only 69 percent, a figure lower than that of more current operative results.[3,15–17] Finally, there was a nonadherence rate in the medical group of 12 percent (most underwent operation after randomization) and in the surgical group of 5 percent. These high nonad-

* The general data for the Veterans Adminstration study can be found in the cited references.[1,2] However, the precise numbers contained in this manuscript are based on updated information kindly supplied by the authors.

herence rates pose formidable problems in the statistical interpretation of the study data.

Possible limitations of the Houston St. Luke's Episcopal-Veterans Administration Hospital study: Problems raised by patient selection factors also exist in the second major prospective randomized study in progress, that from the Houston St. Luke's Episcopal-Veterans Administration Hospital.[3,4] As of late 1977, a total of 60 patients were randomized into the medical group and 56 into the surgical group. The study has reached its 5th follow-up year and the mortality rate is 18 per cent in the medical group and 9 per cent in the surgical group. Although this difference is not statistically significant, the twofold greater mortality in the medically treated patients may exert a substantial influence on the decisions of physicians responsible for advising a patient on operation.*

However, the authors as yet have not published data regarding angiographic findings or an analysis of how many patients had left main coronary disease. This is an important point, because if the study contains a substantial number of patients with left main coronary artery disease, study results would be biased in favor of surgical treatment.[2,18] In addition, 48 percent of the medically treated patients manifested "unstable angina" during the follow-up period. This incidence of unstable angina identifies the patients chosen for this study as a highly selected subgroup.

Applicability of Veterans Administration randomized studies to other patient populations: The Veterans Administration and Houston studies are the best available that allow reliable comparison between the results of surgical and medical therapy. However, although each study presents a valid comparison between two groups of randomized patients with equivalent distribution of baseline variables, questions inevitably arise as to the applicability of the results to other patient populations. In particular, both studies contain an unusually high proportion of patients with symptomatically severe disease. This is an important consideration because, although randomization provides for two treatment groups that at the start of study have equal susceptibility to future events, randomization does not deal with the problem of whether similar results would derive from a study in which patients with different levels of susceptibility to future events were randomized.[11] In other words, can the results of these studies, based largely on severely symptomatic patients, be applied to a mildly symptomatic population?

The results of the Veterans Administration and Houston studies should constitute an important part of the information matrix on which current therapeutic decisions are based. Nevertheless, one can raise serious questions about the appropriateness of their use as the sole arbiter of whether operation is indicated in the asymptomatic or mildly symptomatic subject with coronary artery disease.

*The most recent update of this study[17a] indicates a mortality rate of 20 percent in the medical group and 14 percent in the surgical group after 5½ years of follow-up.

Nonrandomized Studies

These problems, particularly those related to the results and conclusions of the Veterans Administration Collaborative Study, led to a renewed interest in using nonrandomized data to determine whether coronary bypass surgery prolongs life. Most,[7,16,19–21] but not all,[22] such studies appeared to demonstrate a favorable effect of surgery on one or more subgroups of patients with coronary artery disease.

The most recent, and also the most compelling and comprehensive, example of this approach is the article by Hurst et al.[7] These investigators compared the survival statistics of several studies of patients with coronary artery disease who were not treated surgically with the survival statistics of patients undergoing bypass surgery at other institutions. The analysis appeared to indicate very clearly that long-term survival of patients with double or triple vessel disease who undergo coronary bypass surgery is greater than that of patients who do not. The data leading to such a conclusion can be summarized as follows. In general, among patients studied with angiography but not operated on the annual mortality rate is about 1 to 2 percent for those with single vessel coronary disease, 7 percent for those with two vessel disease and 11 percent for those with three vessel disease. The overall mortality rate is about 8 percent.[14,23–30] Surgically treated patients with two or three vessel disease have substantially lower annual mortality rates, averaging approximately 3.5 to 6 percent. The overall annual mortality rate of surgically treated patients is about 2 to 5 percent[3,15,19,31–41] (Table I).

TABLE I

Average Annual Mortality in Patients With Coronary Artery Disease With No or With Mild Symptoms Not Operated on Compared With That of Surgically Treated Patients From Several Institutions

Institution	Type of Patient	Average Annual Mortality	
		Total	2 or 3 Vessel Disease
National Institutes of Health[44]	Asymptomatic-mildly symptomatic, not operated on	1.5%	2.0%
New York University[19]	Operative	4.0	*
New York University[39]	Operative	2.4%	*
Baylor[33,34]	Operative	2.0%	*
Peter Bent Brigham[32]	Operative	2.3%	*
Buffalo General[36]	Operative	2.0%	*
Massachusetts General[35]	Operative	2.4%	*
Emory[7]	Operative	3.0%	*
Cleveland Clinic[37]	Operative	3.3%	4.6%
University of Southern California[40]	Operative	3.3%	3.7%
Stanford University[41]	Operative	5.0%	6.0%

* Data unavailable.

Limitations of nonrandomized studies: The data presented by these types of analysis, suggesting that surgery prolongs life and therefore should be offered to all patients with two or three vessel coronary disease (as well as those with left main coronary artery disease), seem compelling. However, Chalmers et al.[9] pointed out the powerful effect that selection factors exert on conclusions when a control group is not assigned at random. They also emphasized the critically important point that differences in outcome between two groups "matched" for disease severity (that is, number of vessels narrowed) but not randomized, may still occur. They concluded that ". . . these and other indicators of outcome that are less easily measured can be distributed fairly only if the treatments are assigned at random."

These considerations appear extremely relevant to the conclusion of Hurst et al.[7] that ". . . we have adequate evidence that bypass surgery prolongs the life of patients with left main coronary arterial obstruction and triple or double vessel obstruction . . . ." This statement relies on the assumption that the medically treated patients with double or triple vessel disease previously reported on[14,23–27] can be used as a control group for surgical series. However, virtually all published natural history studies of patients with angiographically documented coronary artery disease are derived from large medical centers to which more seriously symptomatic patients are usually referred. Most of these series also were based on patients studied and followed up in the late 1960's and early 1970's and who, for one reason or another, were not judged to be suitable candidates for operation. The critical question therefore arises: Given comparable severity of coronary arterial narrowing, is the natural history of the asymptomatic or mildly symptomatic patient identified and treated today similar to that of the more severely symptomatic patient identified and treated 5 or 10 years ago, so that *prophylactic* operation is warranted?

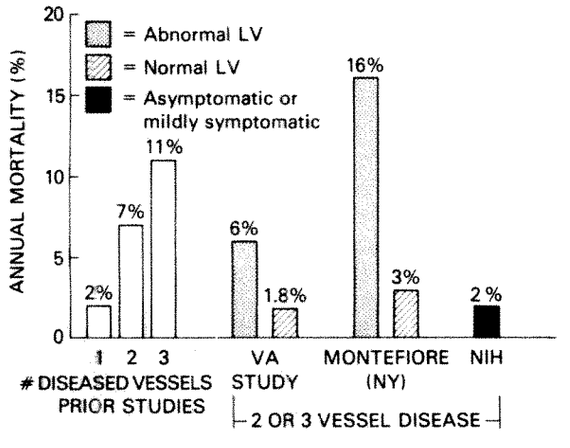


FIGURE 1. Survival in patients with coronary artery disease. "Prior studies" (**open bars**) denote approximate average values derived from Ref 21 to 29. Data from "VA STUDY" are from Ref 42, data from "Montefiore" study from Ref 43 and data from National Institutes of Health (NIH) study from Ref 44. CAD = coronary artery disease; LV left ventricle.

Natural History of Asymptomatic or Mildly Symptomatic Patients With Coronary Disease

Left ventricular function as predictor of prognosis: Support for the view that the annual mortality of the mildly symptomatic or asymptomatic subject is less than that of the more severely symptomatic patient is provided by two recent investigations. Both of these confirm the results of an earlier study from the Cleveland Clinic,[14] which demonstrated that the state of left ventricular contractile function is an important predictor of prognosis, independent of the number of vessels narrowed. Thus, the Veterans Administration Collaborative Study[42] showed that medically treated patients with good left ventricular function had an excellent prognosis even in the presence of two or three vessel disease. The annual mortality rate of patients with two or three vessel coronary disease but with good left ventricular function was only 1.8 percent. In contrast, the annual mortality rate was 6.0 percent in patients with multivessel disease and abnormal left ventricular function. Similarly, a study from Montefiore Hospital in New York[43] demonstrated that, whereas patients with depressed ejection fraction and significant stenoses involving two or more coronary arteries had a relatively poor prognosis (annual mortality rate 16 percent), patients with good left ventricular function had a good prognosis (annual mortality rate 3 percent) even with significant stenosis of two or three vessels (Fig. 1).

Role of prophylactic surgery in mildly symptomatic patients with two or three vessel disease: These results bear importantly on the question of "prophylactic" operation for patients who are asymptomatic or have only mild symptoms. About 75 percent of such patients have good left ventricular function (ejection fraction 50 percent or greater)[44] and therefore would be expected to have a good long-term prognosis. This expectation has been substantiated by the results of the National Heart, Lung, and Blood Institute—Cardiology Branch Prospective CAD Natural History Study.[43] All patients referred for the evaluation of coronary artery disease were admitted to study if they had angiographically documented narrowing of 50 percent or greater in one or more major coronary arteries; symptoms, if present, were mild and well controlled on medical management. Patients with significant narrowing of the left main coronary artery were excluded from study. Eighteen percent of the patients were asymptomatic, and the remaining patients were in functional class II. Forty-three percent had 50 percent or greater narrowing of two and an additional 30 percent had such narrowing of at least three major coronary arteries. Seventy-three percent of all the patients within these two groups had an ejection fraction of 50 percent or more. The patients have been followed for up to 4 years (mean 2 years). The annual mortality rate has averaged only 2.0 percent per year in all patients with double or triple vessel disease (Fig. 1).

Thus, a convincing argument favoring the concept that surgery enhances survival can be constructed when survival of patients operated on is compared with older natural history data derived from patient populations

that are highly selected and appear to consist largely of severely symptomatic persons. However, the argument is not convincing when survival of patients operated on is compared with recent natural history data on the mildly symptomatic or asymptomatic patient. Table I shows that the average annual mortality rate of mildly symptomatic or asymptomatic patients who are not surgically treated is apparently lower than the average annual mortality rate of patients operated on at the institutions[7,19,32–37] cited by Hurst et al., who considered that the data provided evidence establishing that surgery prolongs life. Additional studies serve to substantiate this point.[39–41]

Most of the surgical data cited in Table I are based on results in patients operated on in the first half of the 1970's; hence, it is possible that better long-term survival will occur in patients operated on more recently. Nonetheless, the existing nonrandomized data, and the lack of convincing documentation of a beneficial influence of operation on mortality in symptomatic patients randomized to treatment,[1] indicate to us that the demonstration of coronary stenoses, even if two or three coronary vessels are involved, should not be interpreted as sufficient reason to procede with operation in the absence of left main coronary disease or significant symptomatic limitation.

In addition to these considerations, potentially deleterious effects of operation must be weighed by the physician considering the pros and cons of prophylactic operation. These effects are summarized in the next section of this review.

Long-Term Effect of Coronary Bypass Operation: Late Symptoms and Bypass Graft Patency

Late operative results, including graft patency and symptoms, are particularly pertinent to the question of whether to operate on asymptomatic or mildly symptomatic patients who, as indicated, appear to have a relatively good long-term prognosis.

Graft patency: Several studies have demonstrated that graft patency in the first 6 to 12 months after operation is about 75 to 90 percent,[3,13,15–17,38] and that grafts that are patent 6 months after operation remain patent for the next 2 to 3 years.[45,46] However, if operation is to be undertaken as a "prophylactic" procedure, there should be some assurance that grafts will remain patent for many years.

Such information has only recently become available. In a study from our laboratory,[47] 22 of 30 patients studied as nearly consecutively as possible were evaluated. All had had coronary artery bypass grafting 5 to 7 years previously and had at least one graft patent at early postoperative study. Of the 33 grafts patent at early study, 94 percent were patent at late study. Similar results from the Montreal Heart Institute[48] were recently published in preliminary form. Hence, 75 to 90 percent of grafts are patent within the 1st postoperative year, and most of the grafts will remain patent for at least another 5 to 7 years. These early and late results are extremely encouraging for the patient who needs operation because of severe symptoms. However, the fact that 15 to 30 percent of grafts will become occluded by 5 to 7 years after operation (10 to 25 percent early and 5 percent late) raises some questions as to the wisdom of prophylactic operation in the asymptomatic or mildly symptomatic patient.

Late symptoms due to progression of coronary artery disease: Progression of disease within the native coronary vessels also presents some problems for the prophylatic approach to operation. All 22 patients in the National Heart, Lung, and Blood Institute long-term study of coronary artery bypass grafts[47] were in functional class III or IV preoperatively. Early in the postoperative period, 16 became free of symptoms (class I) but 11 of these (69 percent) exhibited deterioration of at least one functional class over the next 5 to 7 years. Progression of disease in ungrafted vessels accounted for symptomatic deterioration in 9 of these 11 patients, with only 1 of the 11 demonstrating graft occlusion. Similar results were reported in abstract form from the Montreal Heart Institute[48] and from Stanford.[49] Thus, although most patients improve symptomatically after operation, symptomatic deterioration is common in the succeeding years, and this is most often due to progression of disease in ungrafted vessels.

This finding might suggest that a more effective prophylactic operation necessitates grafting of all stenotic vessels, including those with mild (less than 50 percent) stenosis. However, the long-term patency of grafts to vessels that are not critically narrowed is unknown. Because of flow competition, it is possible that graft occlusion would occur relatively frequently.

Perioperative myocardial infarction and graft induced proximal coronary occlusion: Two additional points are of concern. Perioperative myocardial infarction occurs in approximately 5 to 35 percent of patients undergoing coronary bypass surgery.[13,50–55] Although the significance of such damage is not definitely known, there is evidence suggesting that perioperative infarction may deleteriously influence long-term prognosis.[56] Moreover, the operative procedure appears to increase the rate of progression of proximal occlusion in the native coronary vessels receiving such grafts.[57–60] New occlusions could therefore further compromise myocardial flow in those patients whose grafts do not remain patent.

Thus, operatively induced myocardial damage and graft-induced acceleration of proximal occlusion might offset any possible benefit prophylactic operation would have in enhancing survival in asymptomatic or mildly symptomatic patients. In addition, when patients become symptomatic due to spontaneous development of progressive occlusive disease involving coronary arteries that had not been bypassed, the risks involved in *re*-operation may be significantly increased by the prior procedure.[61] The net effect on long-term survival of prophylactic operation has to include the risks of possible additional operations, as well as the risks imposed by operatively induced myocardial damage.

Attempts to Identify High Risk Subgroups

The considerations just mentioned cast doubt on the value of coronary bypass surgery in asymptomatic or

only mildly symptomatic patients. However, it is possible that appropriate examination techniques may identify subgroups within this patient population at high risk of a catastrophic event, which might be averted by prophylactic operation.

Asymptomatic Subjects

In the Seattle Heart Watch study, Bruce et al.[62] found that among 2,760 men initially free of heart disease, there was an incidence rate of sudden cardiac death of only 0.05 percent/year. Maximal exercise testing identified 3.5 percent of the population with a seven times greater risk of *any* coronary heart disease event (angina, myocardial infarction and death). Comparable data relating to sudden death itself are not, unfortunately, available. However, the practical implications of a program designed to identify asymptomatic subjects who may be at high risk of sudden death can be roughly approximated by assuming that exercise testing can similarly identify a subgroup at seven times greater risk of sudden death. Using these approximations, one can calculate that 10,000 asymptomatic subjects, with an annual mortality rate of 0.05 percent/year, would have to undergo exercise screening to identify a high risk group containing *one* asymptomatic subject at risk of sudden death over the course of 1 year (Fig. 2). The exercise screen would yield a group of 350 men (3.5 percent of the population) at seven times the risk of sudden death as the remainder of the population. In this group of 350 men, 1 will be destined to die (0.29 percent/year annual mortality rate).

PRACTICAL IMPLICATIONS OF EMPLOYING AN EXERCISE SCREEN TO IDENTIFY ASYMPTOMATIC SUBJECTS AT RISK OF SUDDEN DEATH

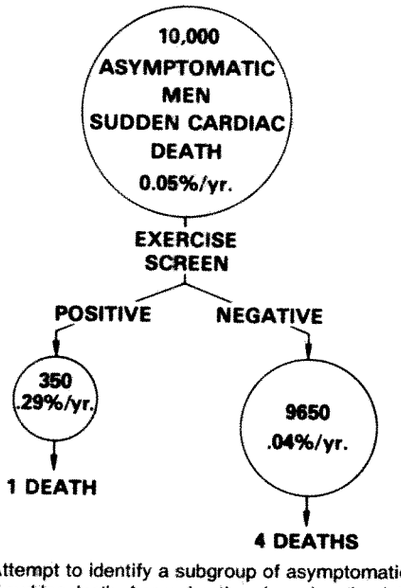


FIGURE 2. Attempt to identify a subgroup of asymptomatic subjects at high risk of sudden death. Approximations based on the data of Bruce et al.[62] and reprinted with permission of the American Heart Association, Inc.

Role of exercise testing for screening patients at increased risk: How can this 1 subject be selected from the remaining 349 men who will not die? Clearly, there must be an answer to this question if such a screening approach can be translated into therapeutic action, because it would be medically unwise to institute aggressive treatment for the 99.7 percent of men who are not at risk of sudden death. Hence, additional screening studies would have to be carried out. Assuming the cost of an exercise screening study is $100, it would cost $1 million (10,000 × $100) to identify a "high" risk subgroup containing one subject who will die in the next year, and additional hundreds of thousands of dollars for the added screening studies. Even if this expensive approach were successful, the much larger "low" risk subgroup would contain four (or 80 percent) of the patients destined to die, none of whom would have been so identified by screening studies. Thus, until more effective screening studies are available for an asymptomatic population, it would be impractical to think of using exercise testing for the purpose of preventing sudden coronary death in this group.

Symptomatic Patients

Measurements of exercise capacity, S-T segment depression (particularly in relation to the intensity of exercise at which S-T segment depression occurs) and reduced increase in blood pressure during exercise,[63,64] as well as detection of complex ventricular arrhythmias during ambulatory electrocardiographic monitoring,[65,66] have each identified patient subgroups at increased risk of coronary death. However, the high risk subgroups thus far identified all contain severely symptomatic patients or those with evidence of abnormal left ventricular function.[67] Thus, although several promising directions are being explored, we still do not have an accurate means of selecting a high risk subgroup from the patient population with stable coronary artery disease and no or mild symptoms. The only possible exception to this statement that most physicians would probably accept is identification of the patient with significant narrowing of the left main coronary artery. Because the only patients in the Veterans Administration Collaborative Study with greater longevity after operation were those with left main coronary arterial narrowing,[2] the question arises whether all patients with coronary disease should be screened for disease of the left main artery regardless of symptomatic status.

Should all patients with coronary disease be screened for left main artery disease? Unfortunately, this question is not readily answered on the basis of empirical information. Studies on the medical versus surgical treatment of left main coronary artery disease were all performed in highly symptomatic subjects. In the population of patients with left main disease defined by the Veterans Administration Cooperative Study, 60 percent were in functional class III or IV and 36 percent of the medically treated patients died after 48 months of follow-up. In the recent nonrandomized study from the Montreal Heart Institute,[68] in which surgery was

found to enhance survival in patients with left main coronary arterial narrowing, 48 percent of the patients not operated on had either unstable angina or were judged to be in functional class III or IV, and 51 percent died after 5 years of follow-up. In addition, 77 percent of the 141 patients with left main disease studied at Cleveland Clinic[69] had class III or IV symptoms (overall annual mortality rate 10 percent), and 94 percent of the 187 patients studied at Duke University[18,70] had either pain at rest or abnormal left ventricular function (overall annual mortality rate 17 percent).

Whether or not less symptomatic subjects share a similarly dire prognosis, which is also improved by operative intervention, has not been established. However, it is of some relevance to note that even when mortality estimates are based on "low risk" patients with left main coronary artery disease, the long-term outlook for medical management is not good. Thus, in the study from the Montreal Heart Institute[68] the 5 year survival rate was about 20 percent in patients treated medically who had an ejection fraction of less than 45 percent, about 40 percent in those with an ejection fraction of 45 to 59 percent but only about 70 percent (6 percent annual mortality rate) in those with an ejection fraction of 60 percent or better. Likewise, in a recent study from Duke University Medical Center,[18] patients with left main coronary artery disease identified as a "low risk subgroup" still had a 3 year survival rate of only 74 percent (annual mortality rate 9 percent). Finally, patients with left main arterial obstruction and normal ventricular function studied at the Cleveland Clinic[69] had a 5 year survival rate of 55 percent (annual mortality rate 9 percent).

Is operation warranted in all patients with significant left main coronary artery disease? Although the natural history of patients with left main coronary artery disease who are considered to be at relatively "low risk" does not appear good, it is not at all clear whether surgery increases survival even in all severely symptomatic patients with left main coronary arterial narrowing. For example, operation may benefit only patients with mild impairment of left ventricular function, and not those with normal function or severe dysfunction.[2,68] Also, the role of coexistent narrowing of the right coronary artery or the degree of narrowing of the left main artery (50 to 70 percent versus 70 percent or greater) in determining relative prognosis is also uncertain.[2,18,68,69] Thus, although the weight of evidence favors operating on the patient with significant narrowing of the left main coronary artery, there remain many uncertainties as to whether an operative approach is warranted in all such patients. However, these uncertainties will probably never be satisfactorily resolved because it is highly unlikely that another randomized study of patients with left main coronary arterial narrowing will ever be carried out.

On purely theoretical grounds, lesions of the left main coronary artery are unique in the extent of myocardium jeopardized and the paucity of opportunity for the development of compensatory collateral blood flow. Thus, rapid progression of such lesions might be expected to produce a relatively high incidence rate of catastrophic events even in patients with few antecedent symptoms. These considerations represent the principal justification for identification and prompt operative treatment of significant lesions of the left main artery in patients with coronary artery disease who lack severe symptoms.

The Search for Left Main Coronary Artery Disease

Left main coronary arterial stenosis is necessarily an angiographic diagnosis. Because coronary angiography is both invasive and expensive, one would prefer to perform angiography only in patients with a high likelihood of significant left main lesions. Such lesions are probably present in about 5 to 10 percent of patients with coronary disease who have symptoms that are stable.[2,18,44,71–74] Although data are lacking, it is likely that asymptomatic subjects with coronary disease have an even lesser prevalence of left main coronary arterial lesions. Thus, a practical noninvasive screening test to identify a subgroup with greater probability of left main coronary artery disease might be particularly useful. However, the large number of subjects in need of screening would make cost an important consideration even if one had an ideally efficient screening procedure.

Asymptomatic patients: In essence, the search for left main coronary artery disease is the search for a subgroup of persons at high risk of sudden death. The enormous medical and economic problems inherent in screening asymptomatic subjects, as discussed previously, indicates the impracticality of mounting a feasible screening effort in such patients, given existing diagnostic technology.

Symptomatic patients: A rough idea of the problems inherent in identifying the mildly symptomatic patient with left main coronary artery disease, and the costs of a less than perfect screening test, are outlined by the calculations contained in Table II. The *minimal* cost, using an ideal screening test that would identify all patients with left main coronary artery disease and yield no false positive results, would be $2,000 per left main stenosis diagnosed.

Role of exercise electrocardiography: In practice, no screening test has yet been devised that approaches the ideal just presented. Although other techniques may eventually prove useful in this regard, exercise electrocardiography is the one screening method that has received widespread acceptance. The relative advantages and disadvantages of exercise electrocardiography are strongly dependent on the extent of abnormality accepted as "positive" (that is, evidence of a need for angiography) for detecting left main coronary disease, and the sensitivity and predictive accuracy of exercise electrocardiography in detecting left main coronary disease. Using data derived from studies of 156 asymptomatic or mildly symptomatic patients with significant coronary disease,[44,71] we found that 9 percent

TABLE II

Relative Efficacy and Cost of Strategies for Detecting Left Main Coronary Stenosis*

Angiographic Criteria	Percent With Left Main Disease: Selected for Angio	Percent With Left Main Disease: Not selected for Angio	Percent of CAD Patients Undergoing Angio	Percent Left Main Disease Detected	Cost† per 1,000 CAD Patients	Cost †per Left Main Stenosis Diagnosed	Cost‡ per 4 Year Survivor
Positive "ideal" screening test§§	100%	0%	10%	100%	$ 200,000	$ 2,000	$40,000
≥2 mm ST↓‖	32%	5.9%	16%	50%	$ 260,000	$ 5,200	$50,600
≥1.5 mm ST↓	23%	4.2%	31%	71%	$ 410,000	$ 5,800	$52,900
≥1 mm ST↓	20%	1.3%	47%	93%	$ 570,000	$ 6,100	$53,800
All patients with CAD	10%	—	100%	100%	$1,000,000	$10,000	$67,700

* Assumptions: prevalence of left main stenosis = 10%; angiography costs $1,000/patient; exercise electrocardiography and the "ideal" screening procedure each cost $100/patient.

† Cost is calculated from the cost of the screening studies performed in all subjects, plus the cost of coronary angiography performed in those subjects with a positive screening test.

‡ Based on assumption that operation increases 4 year survival in almost 3 of every 10 patients with left main disease (4 year survival 64 percent of medically treated, 93 percent of surgically treated[2]) and that coronary bypass surgery costs $10,000.

§§ An "ideal" screening test would identify all patients with left main coronary artery disease and yield no false positive results.

‖ The sensitivity and predictive accuracy data on which these calculations are based were derived from exercise studies terminated when 85 percent of maximal predicted heart rate was reached, or at onset of symptoms, whichever appeared first. Different statistics would undoubtedly apply (greater sensitivity but *lower* predictive accuracy) if a symptom-limited protocol were employed.

Angio = angiography; CAD = coronary artery disease.

had 50 percent or greater narrowing of the left main coronary artery. S-T segment depression of 2 mm or more identified a subgroup of candidates for angiography with a relatively high proportion (32 percent) of left main coronary artery disease. However, in about 50 percent of patients with occlusions of the left main artery 2 mm or more S-T segment depression did not develop and thus their condition would have gone undiagnosed. S-T segment depression on exercise of 1 mm or more identified a subgroup of candidates for angiography of whom 20 percent had left main coronary artery disease. Thus, although the yield of left main coronary artery disease was thereby increased (with only 10 percent of patients with such disease having a negative exercise test) as compared with the unscreened population, the cost of diagnosing left main coronary artery disease using such a screening procedure would be only about 35 to 40 percent below the cost that would be expended for a program to perform angiograms in all symptomatic patients with coronary disease.

Role of surgery in prolonging life: Finally, about 6 of 10 patients with left main coronary artery disease who are not operated on survive 4 years, and operation increases this number by only 3, to 9 of 10 patients.[2] A program of screening for and operating on patients with left main coronary artery disease could succeed therefore in prolonging life for 4 years in, at most, 3 of every 10 patients identified and it may yield even more modest results in mildly symptomatic patients with mostly normal ventricles and a better prognosis. Hence, the cost per 4 year *survivor* (assuming a cost of $10,000 for coronary bypass surgery) would be more than $50,000 for those selected for angiography because they had 1 mm or more S-T segment depression on exercise stress testing, and it would be more than $65,000 if all patients with coronary artery disease underwent angiographic study (Table II).

Implications of left main coronary disease: From these rough calculations, it would appear that a large scale screening program, designed to detect and operate on mildly symptomatic coronary patients with left main coronary artery disease, would be prohibitively expensive. However, it is probably unrealistic to expect a physician to make medical decisions regarding his individual patients on the basis of the economic impact that decision will have on society as a whole, should that decision be applied in all similar instances. Resolution of the problem posed by a consistent "preventive medicine" approach to left main coronary artery disease is extremely difficult, if not impossible, given the basic conflict between individual patient benefit and prohibitive costs to society. In this regard, it should also be pointed out that although sudden death does occur in an asymptomatic or mildly symptomatic population, it is possible that only a small proportion of such deaths occur in patients with left main arterial stenoses.[75] Indeed, in a recent study from Finland, Rissanen and coworkers[76] found that of 151 sudden deaths from coronary artery disease occurring outside of hospital, only 5 percent had 50 percent or greater narrowing of the left main coronary artery.[76] This prevalence of left main disease is similar to that determined by angiographic studies in living patients, raising the possibility that patients with left main disease are not at appreciably higher risk of sudden death than those with double or triple vessel disease.

A Suggested Strategy for Evaluation and Surgical Treatment of the Patient With Coronary Disease

Incomplete data currently available prevent the synthesis of a consistent and scientifically defensible strategy for the evaluation and treatment of all patients with coronary artery disease. Although many relevant facts have emerged over the past several years, remaining uncertainties have provided a fertile environment for the propagation of diverse strategies, without one qualifying as the "correct" approach. Nonetheless,

decisions must be made by the clinician, even though definitive data are unavailable. On the basis of our analysis, we have formulated a practical strategy for evaluating patients with coronary artery disease that seems reasonable. However, we realize that there will always be exceptions, depending on an individual patient's desires, emotional response to his illness, role expectations, plans for the future and, unfortunately, his financial resources.

Patients with symptoms refractory to medical therapy: The patient whose life style is unacceptably restricted by angina, despite medical therapy, is a candidate for coronary bypass surgery. Cardiac catheterization should be performed and the patient operated on if he or she is found to have suitable coronary arterial anatomy and left ventricular function.

Patients with mild symptoms or previous major complication of coronary artery disease: If a patient on optimal medical therapy has mild symptoms of coronary artery disease, or has had a previous myocardial infarction, we recommend coronary and left ventricular cineangiography. Based on the cost-efficiency analysis presented in Table II, it might be reasonable to perform catheterization only in those patients with symptomatic coronary disease who have 1mm S-T segment depression or more during exercise, using a protocol in which exercise is stopped at symptoms or when 85 percent of maximal heart rate is achieved. Operation is offered to patients discovered to have significant disease involving the left main coronary artery; the remaining patients are treated medically.

Patients with no symptoms of coronary artery disease: We do not believe it is medically or economically practical to screen such patients for coronary artery disease. However, many asymptomatic subjects come to attention because of a positive electrocardiographic exercise test performed as a routine part of an annual physical evaluation. This group presents the physician with a dilemma. Whereas 10 percent of *asymptomatic* men over age 40 years will have 1 mm or more S-T segment depression on electrocardiographic exercise stress testing,[77-80] only about one third of these subjects have 50 percent or greater stenoses as determined with angiography.[81,82] Although definitive data are unavailable, the prevalence of left main coronary arterial stenosis in such a population is probably not very great. More important, the data from the Seattle Heart Watch Study[62] previously quoted indicate the impracticality of identifying the individual asymptomatic high risk patient. Because of the resulting low yield of left main coronary lesions that will be discovered, and the difficulty inherent in identifying the individual asymptomatic patient at high risk, we do not routinely perform cardiac catheterization in such persons. We normally treat risk factors as vigorously as possible whenever these are detected, in the hope of retarding progression of disease or preventing its occurrence.

Conclusion

Conflicting facts and hypotheses, deficiencies of crucial information and, more recently, increasing concern for the financial impact of medical decisions on a society whose financial resources are not limitless have created much confusion regarding the role of surgery in patients with coronary artery disease. To us, these considerations justify a cautious approach to the treatment of such patients. Our orientation is based on the premise that the coronary bypass operation, an expensive procedure that carries with it a small but definite risk, should not be generally applied to all patients with coronary artery disease until an adequate factual basis can be marshalled to justify such use.

We believe, on the basis of the preceding analysis, that at present the only patients who should undergo coronary bypass surgery are those whose symptoms, despite medical therapy, significantly interfere with their leading a happy and productive life, and those who have significant narrowing of the left main coronary artery. Although there will always be exceptions, we do not believe it is justified to offer operation to the asymptomatic subject with coronary disease or to the patient whose symptoms are well controlled with medical treatment and whose disease does not involve the left main coronary artery. Perhaps, in the near future, additional studies of risk predictors may lead to detection of high risk subgroups within the mildly symptomatic population. If such subgroups can be identified, the indications for operation may be broadened.

The question of how the patient with left main coronary artery disease can be identified raises formidable cost problems. From a strictly medical point of view, we believe it would be reasonable to perform coronary angiography on all patients with symptomatic coronary disease. The justification of this approach is that the risks are minimal and that it is the only technique at present that can unequivocally identify the patient with left main coronary artery disease. At the same time, we recognize the socioeconomic dilemma created by such an approach, in that the resulting financial burden to society would be prohibitive if angiography were offered to all symptomatic patients with coronary artery disease. Exercise testing may offer a reasonable compromise, in that it appears capable of detecting all but about 10 percent of symptomatic patients with left main coronary stenoses. The saving in cost and utilization of angiographic facilities is not insubstantial. However, it would be unrealistic to assume that even this economizing approach presents a financially feasible alternative because the costs of screening for and operating on all patients with left main coronary artery disease would still be prohibitively expensive. Moreover, this approach would probably not have an important overall impact on the incidence of sudden death from coronary artery disease because the huge majority of patients with coronary disease who die suddenly do not appear to have left main coronary artery disease.[76] Clearly, more effective noninvasive techniques must be developed that will permit economical and accurate identification of mildly symptomatic subjects at high risk of sudden death.

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Historical Development of Concept of Blood Circulation

An Anniversary Memorial Essay to William Harvey

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One of the most significant contributions to medicine—William Harvey's concept of the circulation of the blood—was quietly announced early in the 17th century with the publication of a book, *De Motu Cordis*. This book, a culmination of thought, observation and controlled testing with conclusions based on the results of repeated experiments, changed the course of medical thinking.

The year just ended, 1978, presented at least two excellent reasons to commemorate and to honor William Harvey. First, Harvey was born on April 1, 1578, and we celebrated the 400th anniversary of his birth; second, 1978 also marked the 350th anniversary of the publication date of his epoch-making classic, *De Motu Cordis*.

Truly a bold man, indeed, O
disturber of the Quiet of Physicians!
—Zachary Wood

On June 3, 1657 death came to the great figure who unlocked the door for today's cardiovascular research. That man was William Harvey (Fig. 1). Early in 1971 two California dealers in rare books together sold for $60,000 a slender, rather unattractive book that had been printed in Frankfort, Germany in 1628 by William Fitzer. This book, containing 72 pages, badly printed on poor paper and in Latin, was written by Harvey. Commonly referred to as *De Motu Cordis*, the book presents his observations and demonstrations relating to his concept of unidirectional circulation of the blood in the body. With this concept and using scientific methodology, Harvey confronted and indisputably refuted what physicians up to that time had generally believed about the heart and the circulation. *De Motu Cordis*, one of the most important works in the history of medicine, helped to transform scientific medicine regarding the human body. Almost every important medical advance in modern times is indebted to this book.

Authors of great ideas have usually not been responsible for the totality of their ideas. To expect this would be to ignore the history of human knowledge. Man has built on the information delivered to him from previous generations to produce a fund of human knowledge. Thus, a great thinker does not start from nothing and construct ideas. He starts with the knowledge of his species and adds to it. The greatness of his contribution and the uniqueness of his synthesis are measures of his genius. The eclectic nature of his contribution does not detract from his greatness. Thus it was with William Harvey. The world of ideas was changed after him and could not return to its previous ways. In an exploration of the contributions of William Harvey it is interesting to survey the ideas that preceded him. We tend to make this kind of survey with little intellectual humility. Thus we can wonder how such a bright man as Aristotle could fail to observe things obvious to us, or why Harvey did not reach his conclusions earlier.

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The history of knowledge of the circulation falls into eras. In the first era, structural aspects were stressed and teachers were concerned with anatomy. In the second, mechanical aspects of the circulation were emphasized, and this was the era of Harvey. More recently, cardiovascular research has been concerned with physiology, biochemistry and metabolism. As a result, patients have benefited from measurements of blood volume, cardiac catheterization, use of heart-lung bypass machines and transplantation of organs. For an appraisal of Harvey's contributions, some historical background, starting with primitive man, is essential.

Contributions by Early Man and Ancient Civilizations

Early man: The anatomic and physiologic knowledge of primitive man can be only a matter of conjecture. Animal figures found painted on the walls of caves often showed a heart, and some showed a kind of lifeline from the mouth to the heart.

Egyptian contribution: The ancient Egyptians may have recognized the pulse and may have had some idea of circulation. *The Edwin Smith Surgical Papyrus* seems to recognize the heart as the center and pumping force in a system of distributing vessels. Earlier Egyptian manuscripts mention the heart ("Papyrus Ebers," c 1550 B.C.; "Brugsch Papyrus," c 1300 B.C.); however, both manuscripts describe it as a well from which vessels extend to the limbs.[1,2a]

Chinese contribution: The ancient Chinese seemed to have some understanding of circulation. The *Nei Ching, Internal Classic* or *Canon of Medicine* (authorship is traditionally ascribed to Huang Ti, the Yellow Emperor, 2698–2598 B.C.) contained the following statements:

> The blood current flows continuously in a circle and never stops.
>
> The blood cannot but flow continuously like the current of a river, or the sun and moon in their orbits. It may be compared to a circle without beginning or end. . . .
>
> The blood travels a distance of three inches during inhalation and another three inches during exhalation, making six inches with one respiration.[3]

In spite of these provocative statements, the nature of the pulmonary and systemic circulations was not understood. In one passage in this classic,[3] the bloodstream is described as starting from the foot and circulating to the kidneys, heart, lungs, liver and spleen and from the spleen back to the kidneys.

Greek influence: Information about the heart and vascular system, although incomplete, was known to the Greeks as early as 600 B.C. Alcmaeon of Crotona distinguished between arteries and veins and asserted that the seat of sensation was the brain, not the heart. In the Hippocratic writings and the pseudo-Hippocratic tract, *De Corde* (400 B.C.), the heart was declared to be a muscle. Animal dissection was employed, and the heart was noted to be part of the vascular system. Several observers had noted empty arteries after death. They inferred that arteries normally contained air.[2b,4]

Herophilus of Alexandria used a water clock to time the pulse, and he noted systolic and diastolic phases. He described four properties: frequency, rhythm, size and strength.

Erasistratus of Alexandria (c 310-250 B.C.) described the atrioventricular valves and the chordae tendineae. The semilunar valves had already been described in *De Corde*. His description of arteries and veins is accurate enough to suggest that he dissected human bodies. He described the mode of closure and the purpose of the valves and even postulated a kind of anastomosis between arteries and veins, anticipating the need for the capillary circulation. In spite of these observations he was directed by the ancient Ionian notion that everything in the universe is in a state of flux—that cosmic and organic processes move in cycles.[2d,5] It is important to note that one by-product of the era just before Erasistratus, circa 300 B.C., was the separation, for the first time, of scientific investigation from philosophy.



FIGURE 1. Bronze bust of William Harvey owned by the Mayo Medical Library.

Early Individual Contributors to the Concept of Circulation

Aristotle (384–322 B.C.): Aristotle presented an account of the vascular system, coherent for his day. He described the pericardium and the general outline of the heart but did not mention the valves. He had no clear concept of the circulation, yet he believed that the body was nourished by the blood and that the blood flowed from the heart to the rest of the body where most of it was used up. Some statements in Aristotle's account are accurate and others are grossly wrong. This should not cause surprise. The subject of blood and the function of respiration had been full of mystery and fable since prehistoric times. The wonder is not that things were so wrong but that so many observations were correct. If we consider that a master such as Aristotle was thusly mistaken, it serves to explain the slow learning process of the human species.[2c,6a,7a]

Galen (131–201 A.D.): Galen came from Asia Minor to Rome and exerted tremendous influence throughout the

Western world. As late as 1649 one of his followers (Riolan) said that if findings in subsequent dissections differed from the observations of Galen, then nature must have changed.[2e] However, scholars in the 19th and 20th centuries called him an authority to whom the world owed a perpetuation of fundamental errors that caused arrest in medical development.[7b] Neither point of view is realistic and there is no simple exercise by which one can discover the "real" Galen. He did carry out experiments, dissections and vivisections. He made many observations and many contributions. Yet, in spite of much evidence, he missed the idea of circulation of the blood. He recognized the motion of blood and knew the correct direction of flow at the level of the heart. Somehow he did not recognize the inadequacies of his scheme.

In the 17th century, when Harvey developed arguments about the circulation, they were expressed largely in opposition to Galen. Some of these were accurate accounts of Galen's beliefs and some were not. Galen's theory of the motions of the blood in the heart and lungs was summarized by Fleming as follows[8]:*

> Blood on entering the right ventricle must pass by a one-way valve opening inward, so that only an insignificant portion can relapse into the vena cava whence it came. Some of the blood passes directly from right to left through the interventricular septum. But much, and apparently most, of the blood moves into the arterial vein (our pulmonary artery) past a one-way valve opening outward from the ventricle. On contraction of the thorax, the blood in the arterial vein, its retreat cut off from behind, can only go forward into the arterial system of the lungs (in modern usage, venous).

Galen subsequently abandoned the idea that a significant amount of blood passed through pores in the interventricular septum, although this was accepted for many centuries and was a specific point singled out by Harvey for attack.

Ibn-al-Nafis (c 1210–1288): Ibn-al-Nafis studied medicine in Damascus, where he lived, and in Cairo. He was a physician and excelled additionally in languages, philosophy, Moslem canon law, tradition and rhetoric. He wrote at least 10 books on medical subjects and a volume entitled *The Perfect Man*, in which he expounded a kind of theory of the pulmonary circulation. He was not a biologic experimentalist. He did not engage in dissection because of the prevailing religious laws and an inherent personal compassion. His observations and studies appear to be dependent on Galen's research and records. He had a high opinion of Galen's work.

According to Ibn-al-Nafis, the heart created spirit from thin blood. Blood went to the right side of the heart where it was thinned. It could not pass directly to the left ventricle because openings to permit this did not exist. According to him, the blood flowed from the right ventricle to the lungs and back to the left side where it was concocted with animal spirit and distributed to the organs to animate them. Interestingly, he denied that flow occurred across the ventricular septum because there were no apparent pores, but he was ready to permit the existence of pores in the pulmonary artery (capillaries), although they were no more visible there.

Ibn-al-Nafis was aware of the anatomic facts as was Galen. He stated that blood is made by the liver and passes to the right ventricle. He explained the thick pulmonary artery as Galen did, that is, by the flow of blood from the pulmonary artery to the lungs. Thus, Galen knew that air was essential and that blood flowed from the pulmonary artery to the left ventricle and thence to the entire body. However, he did not develop these ideas and left only a blur regarding the details. Ibn-al-Nafis, using the same information, called attention to the pulmonary circulation. This glare of brilliance was apparently isolated, and this subtle change in emphasis was not noticed or not continued by his own students and associates. The subject was rediscovered 200 years later by someone unfamiliar with Ibn-al-Nafis and his insights.[2g,7c]

Leonardo da Vinci (1452–1519): Leonardo is said to have dissected 30 cadavers and to have made nearly 800 anatomic drawings. He and a friend intended to publish a treatise on anatomy, but this was never accomplished. Most of his drawings were not published until early in the 20th century. He thought of the heart as a pump and believed that the heartbeat and the pulse were synchronous. The drawings were superb, but their influence was late and restricted.[2f]

Michael Servetus (c 1509–1553): Servetus was born in Spain and before he was 21 years of age he managed to offend both the Lutheran and the Catholic authorities in Europe with his theologic treatises. He made few friends and many enemies and went to Paris under a pseudonym. He was engaged for a time as a prosector but his dissections were "conventional and perfunctory." Medically and anatomically he was a traditionalist and a Galenist. He reached his conclusions by intellectual exercise. He was interested mostly in controversy, particularly in religion. The great truth of the pulmonary circulation seems to have occurred to him almost accidentally. Although he published the first description of the lesser circulation, his influence was limited because the book in which he published it was destroyed. The book, primarily a controversial religious text, was opposed by both Catholic and Protestant authorities in Europe, the anatomic text being only a small part of the book. He was executed for heresy in Geneva under the direction of Calvin. Of 1,000 copies of his book, *Christianismi Restitutio* (1553), only 3 still exist.[7d]

Matteo Realdo Colombo (Realdus Columbus) (1516–1559): Colombo succeeded Vesalius as professor of anatomy at Padua. Colombo's single book, *De Re Anatomica* (1559), was based on examination of 1,000 cadavers, according to his statement. It is well organized, and he was cited by Harvey as a master.

Colombo was an observer and an investigator. He thought independently and was willing to follow logic and his investigations to their conclusions. However, he was thoroughly Galenic in his outlook. He believed that the liver perfected the nutrient blood distributed by the veins, that the left ventricle dispatched vitalized blood by way of the aorta and that blood was thinned in the lungs, where it was also aerated. His description of the valves was precise, and he stated that because of the valves it was known that the blood passed through the heart. He noted that the pulmonary artery carried blood to the lungs and the pulmonary vein returned blood mixed with air to the left side. He did not describe any means of demonstrating his claim. He accepted the existence of septal pores and believed that the pulmonary artery originated from the liver and not from the heart.[7e]

Andrea Cesalpino (c 1519–1603): Cesalpino was a student of Colombo's and was thoroughly grounded in anatomy and dissection. Thus it is not surprising that he knew about heart valves and had some understanding of their purpose. He also described the pulmonary circulation, as had Servetus and Colombo. The extent of his contribution to the general understanding of the circulation of the blood is disputed. For some medical historians, he came close to equaling Harvey.

* According to Fleming, Galen's views on the motion of the blood in the heart and lungs have been misconstrued by many historians.

For others, he was another thinker who was interested in a great variety of subjects and who identified his ideas primarily with Aristotle but who never approached the circulation as we know it. In any case it appears that he was the first to use the term "circulation."

The first book containing mention of the pulmonary circulation was *Quaestionum Peripateticarum* (1571):

> Therefore the lung draws the warm blood from the right ventricle of the heart through a vein resembling an artery [the pulmonary artery] and returns it through the venous artery [the pulmonary vein] to the left ventricle of the heart. . . . To this circulation of the blood from the right ventricle of the heart through the lungs into the left ventricle of the same, [the findings] from dissection fully correspond. . . . Thus the whole system is beautifully ordered. Since it is necessary to have heat in the blood of the heart in order to bring about the perfection of the nutriment, . . . blood is transmitted from the right side of the body to the left, partly through the septum and partly through the inner tissue of the lungs, for the sake of being cooled.[7g]

A later book, *Quaestionum Medicarum* (1593), also mentioned veins, arteries and the pulmonary circulation. Cesalpino noted that when a vein was ligated it distended below and not above the ligature. Somehow, in spite of almost the complete concept, he did not draw the conclusion that the bloodstream in the veins always leads to the heart. He continued in his attitude of intellectual servility to Aristotle and could not use even his own research and observations to full advantage. His style is ponderous and vague, which has permitted a group of admirers to claim that he made revolutionary discoveries and teachings in regard to the vascular system. His contemporaries did not regard him in this way and he made no claim to it himself.[2h,6b,7f]

Carlo Ruini (?1530–1598): Ruini, a senator, published a veterinary work, *Dell'Anatomia e Delle Infermita Del Cavallo* [The Anatomy and Diseases of the Horse], shortly before his death in 1598. It describes the pulmonary circulation. He stated that the function of the right ventricle was to propel the blood and nourish the lungs, whereas the function of the left ventricle was to receive the blood from the lungs and send it through the arteries to all parts of the body. He also discussed the valves of the heart and their function in clear, precise and physiologically accurate terms. His book was widely read and republished into the 18th century. Apparently it was read by veterinarians but had had limited appeal otherwise. Its influence on the general field of medicine appears to have been limited.[9–11]

Hieronymus Fabricius ab Aquapendente (1553–1619): Fabricius was a talented and productive scientist. He contributed heavily to embryology and established the foundations of comparative embryology. He was Harvey's teacher of anatomy at Padua. He demonstrated valves in veins and described them carefully. He expressed wonder that they had never been noticed before. (They had been noticed but references were vague and no real attempts had been made to explain their purpose.) Fabricius noted that the veins opened in a direction facing the heart but from this point on the development of the idea was left to his pupils. Fabricius incorporated the veins into his Galenic framework. He believed that valves helped to distinguish the nutritious venous blood and that they acted to prevent dilatation of veins which otherwise would have resulted as blood rushed into areas needing prompt nourishment. He believed that blood flowed outward from the liver and the heart and that some organs lacked valves (in their veins) because they required an uninterrupted supply of nourishment.[7h]

Many of the same Galenic ideas were held by Harvey, and the ideas relating to the true purpose of the venous valves required some years to mature. The next steps seem to us like small ones, and the wonder is, as expressed by Fabricius about the valves, that no one had noticed them before. The fabric of science is formed from many, often minor contributions and by communication. Often the result of a discovery is not noticed or is misunderstood at the time it is made. Each fundamental idea is like a landing in a staircase which fosters new and greater enlargement. Thus it was with Harvey's new concept, which was to have explosive potentialities.

William Harvey

William Harvey, whose memory we honor herein, was born April 1, 1578, in Folkestone, Kent, England. He received his primary education in the grammar school of Canterbury and in 1593 he became a student at Caius College, Cambridge. Dr. Caius, the founder and master of that college, taught Greek. Moreover, he introduced the study of practical anatomy to England and, through his influence, the college was allowed annually to use the bodies of two executed criminals for purposes of dissection. Harvey received his bachelor of arts degree from Cambridge in 1597. Possibly Dr. Caius's teaching of anatomy at Caius College influenced Harvey in the choice of his career, for he decided on medicine. It was probably the fame of Padua's school of anatomy that took Harvey there about 1598. It had been made famous by Vesalius and, in Harvey's time, its fame was perpetuated by Hieronymus Fabricius ab Aquapendente. In *De Motu Cordis*, Harvey referred to Fabricius, his former teacher, as a "celebrated anatomist." Years later Harvey expressed to Robert Boyle, the noted chemist, that the great teacher's work on the valves in veins stimulated him to investigate the mystery of blood circulation.[12]

Harvey, in 1602, received his diploma as Doctor of Physic from Padua. Apparently he had made a good impression on his superiors. In the diploma it stated that he had conducted himself so wonderfully well in the examination and had shown such skill, memory and learning that he had far surpassed even the great hopes that his examiners had for him.

In the same year that Harvey was granted a degree from Padua, he returned to England and received the degree of Doctor of Medicine at Cambridge. In 1604, he settled in London and married the daughter of Lancelot Browne, physician to Queen Elizabeth and James I. In 1607 he was elected a fellow of the College of Physicians and, in 1609, was appointed physician to St. Bartholomew's Hospital. This position he held for 36 years.

In 1615, Harvey was appointed Lumleian lecturer, a highly esteemed position under the sponsorship of the College of Physicians. He continued in this lectureship for 41 years. In 1618 he was appointed physician-extraordinary to James I and, after the death of this monarch, Charles I appointed Harvey physician-in-ordinary. The manuscript notes of his first lectures are

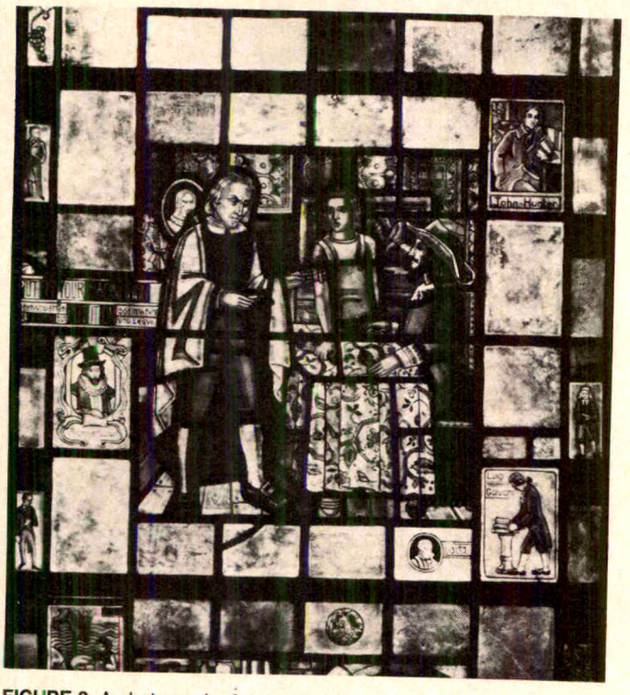
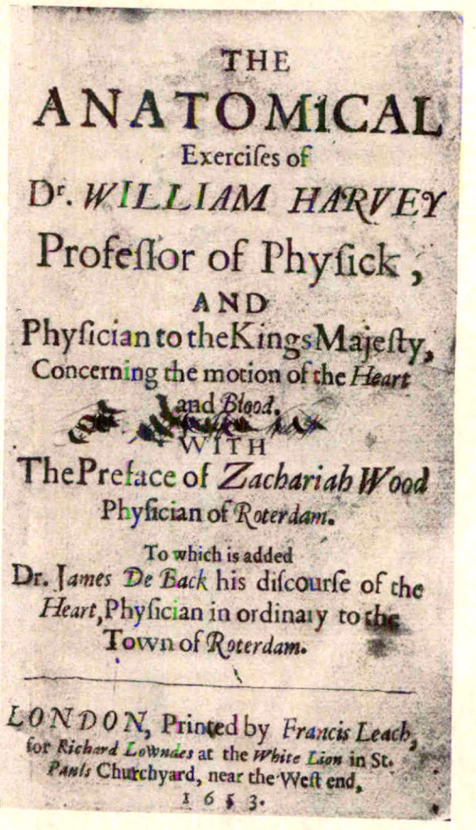


FIGURE 2. A photograph of a panel in the stained glass window on the east wall of Balfour Hall in the Mayo Foundation House in Rochester, Minnesota, the former home of Dr. and Mrs. W. J. Mayo. This panel depicts Harvey demonstrating the heart and the process of circulation to King Charles I. (For a detailed description of the window see Balfour DC, Keys TE: A stained glass window on the history of medicine. Bull Med Libr Assoc 32:488, 1944. [reprinted by permission]).



THE
ANATOMICAL
Exercises of
Dr. WILLIAM HARVEY
Profeſſor of Phyſick,
AND
Phyſician to the Kings Majeſty,
Concerning the motion of the *Heart*
and *Blood*,
WITH
The Preface of *Zachariah Wood*
Phyſician of *Roterdam*.
To which is added
Dr. *James De Back* his diſcourſe of the
Heart, Phyſician in ordinary to the
Town of *Roterdam*.
LONDON, Printed by *Francis Leach*,
for *Richard Lowndes* at the *White Lion* in St.
Pauls Churchyard, near the Weſt end,
1653.

FIGURE 3. Title page of first English edition of Harvey's *Anatomical Exercises*. From copy owned by Mayo Medical Library. (From Harvey W: Anatomical Exercises, Concerning the Motion of the Heart and Blood. London, Francis Leach, 1653.)

now in the British Museum and they have been reproduced in facsimile. These notes reveal that, by 1616, Harvey had dissected more than 80 different kinds of animals and also had developed many preliminary thoughts concerning the heart and the circulation of blood.

Harvey, at least formally, did not publish these early thoughts but continued his teaching programs and research. There is little doubt that at the same time ideas on circulation of the blood were fermenting and crystalizing in his mind as he scientifically confirmed his theories concerning them.

Harvey finally saw fit to publish his great work on the circulation of the blood, and in 1628 in Frankfort his well organized book on this subject was published. (A book fair in that city offered special facilities for publication and good possibilities for a large circulation.) As mentioned by Garrison,[13] this work not only gave proof of the circulation but it was the first quantitative measurement in any biologic investigation and gave impetus to the rise of physiology. The essence of Harvey's remarks was that the blood enters the right side of the heart, is pumped through the lungs to the left side and, from there, is forced through the arteries to the body, returning through the veins to the heart, and the whole process is repeated (Fig. 2).

We shall briefly review Harvey's *De Motu Cordis*, as translated by Leake,[14] which gives the most modern outlook of the various translations.*

In his introduction, Harvey stated that what others had said and what was traditionally believed should be reviewed. Former correct beliefs should be confirmed and incorrect beliefs made right "... by anatomical study, repeated experiment, and careful observation. ..." [14a] Harvey clearly pointed out the relation between function and structure: "Since the movements and structure of the heart differ from those of the lungs, ... separate functions or purposes are likely." [14b] A hint concerning the path of the blood reads: "In cutting open an artery it is equally clear that the blood escapes in one continuous direction. ..." [14c] Harvey demolished the Galenic theory of perviousness of the septum:

* Other English translations include the first, translator unknown, published in 1653 (Fig. 3), and reprinted in 1673 and again in 1928 by the Nonesuch Press; the second, a translation by Michael Ryan, was published in the *London Medical and Surgical Journal*, 1832–1833; a third, by Robert Willis, first published in 1847, and Chauncey D. Leake's translation in 1928. For complete descriptions see *A Bibliography of the Writings of Dr. William Harvey.*[15]

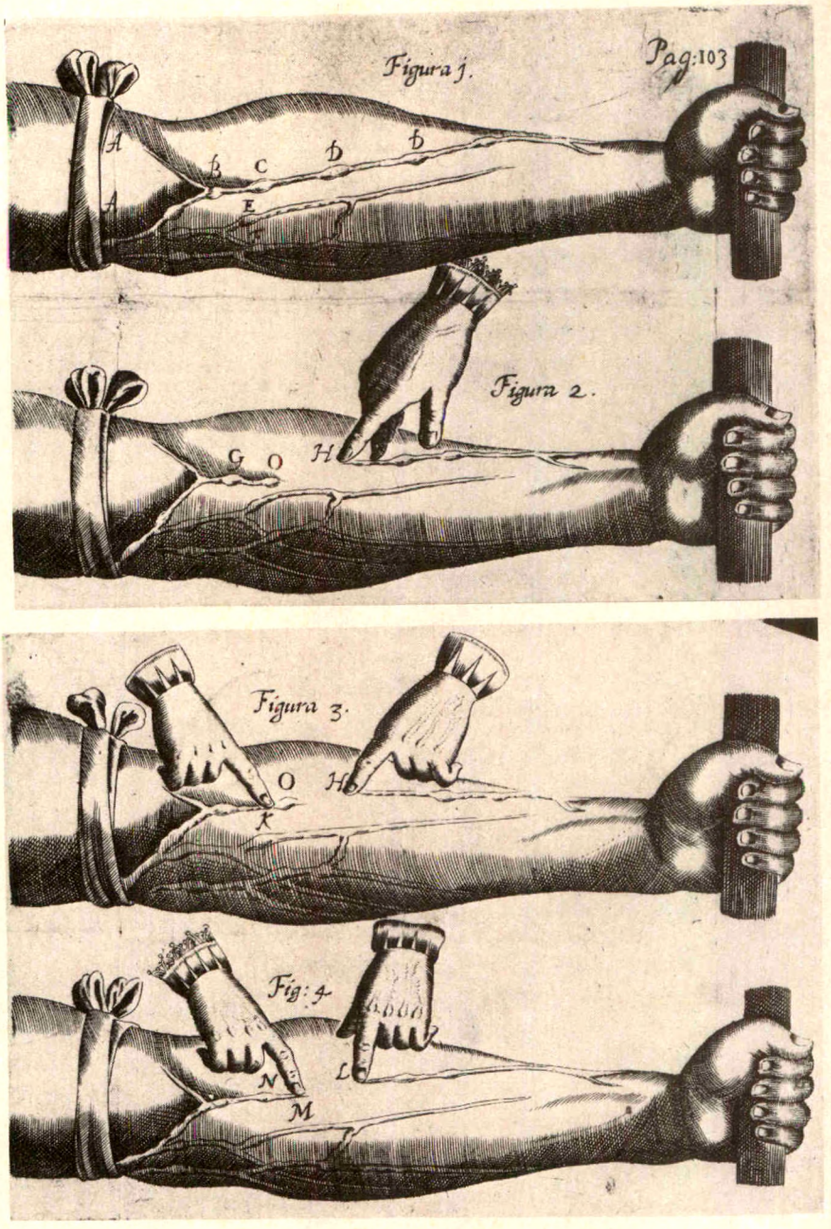


FIGURE 4. Illustrations (Fig. 1 through 4) from folding leaf in Harvey's *De Motu Cordis*. From the 1643 edition owned by Mayo Medical Library.

> The blood is supposed to ooze through tiny pores in the septum of the heart from the right to the left ventricle, while the air is drawn from the lungs by the large pulmonary vein. According to this many little openings exist in the septum of the heart suited to the passage of blood. But, damn it, no such pores exist, nor can they be demonstrated![14d]

A convincing argument for the lesser circulation was presented: "Why require invisible pores and obscure uncertain channels to get the blood to the left ventricle when there is such a wide open passage through the pulmonary vein?" [14e]

In chapter I, Harvey told of the difficulties of cardiac research with which many modern investigators agree. For instance, in animals he could not really tell when systole or diastole took place because of the rapidity of cardiac action. But by meticulous care and repeated experiment he gained accurate information.

In chapter IV, Harvey discussed the motion of the heart and auricles in animals. Here, according to Leake, Harvey issued the first clear statement on the origin and conduction of the heartbeat: "The movement seems to start in the auricles and to spread to the ventricles." [14f]

Chapter VI is devoted partly to consideration of the passage of blood from the right ventricle of the heart to the left. Harvey declared that anatomists made many errors in generalizing from dissections of human bodies

alone and that dissection of lower animals cleared up many perplexing problems.

Chapter VII is on the passage of blood through the lungs from the right ventricle of the heart to the pulmonary vein and left ventricle. The author's reasoning is characteristic: ". . . Nature was compelled, when she wished to filter blood through the lungs, to add the right ventricle, whose beat should force blood from the vena cava through the lungs into the left ventricle." [14g]

In chapter VIII, Harvey published his observation that the heart will pump blood in excess of what can be manufactured from the digested food. Here, too, is definition of the functions of arteries and veins: "The arteries are the vessels carrying blood from the heart to the body, the veins returning blood from the body to the heart. . . ." [14h] Chapter IX also has to do with quantitative determinations.

Chapters X through XII contain the record of how, by vivisection and ligature, the greater circulation was studied and Harvey's view of the necessity for capillary anastomosis. On this latter point, Harvey's work was confirmed in 1660 by Malpighi, who used the microscope. In chapter XIII Harvey explained the true functions of the valves of the veins (Fig. 4).

Harvey's findings are given in chapter XIV, and in chapter XV is his confirmation of the circulation of the blood by plausible methods.

In chapter XVI, circulation of blood is related to the practice of medicine. Harvey believed, for instance, that contagions from wounds were carried by the blood through the whole body.

The circulation of the blood, according to Harvey, also explained why some medicinal agents applied to the skin have almost as much effect as those taken orally. Harvey further stated: "It opens up a field so vast that were I to scan it further or investigate it more fully this little effort would swell to a huge volume which perhaps would take more than my ability or span of life to finish." [14i]

Chapter XVII, the concluding chapter, contains discussion of comparative physiology of the circulation in man and lower animals.

In the blood circulation concept that Harvey conceived of and proved, the only really important missing points were proof of the existence of the capillaries and the knowledge that blood was a vehicle for oxygen.

Harvey's book aroused great controversy in its day. He was severely attacked by traditional thinkers of his time. It is said, also, that his prestige as a physician suffered because of the storm of controversy. Harvey was extremely patient about replying to his critics, ignoring all of them except John Riolan, professor of anatomy at the University of Paris. Keynes's[15] bibliography on Harvey contains a reference to Riolan, who wrote a criticism in 1648, and Harvey replied in 1649. Riolan's views are better stated in his *Opuscula Anatomica Nova* published in 1649. The French anatomist entertained no doubts about the circulation. However, he questioned whether the whole blood or only a portion of it circulated; he raised questions about the speed of its transit and about its passage through the septum and through the substance of the lungs. Riolan was still guarding the ancient medical tradition of Galen. Even though Harvey added more observations to prove his doctrine, Riolan probably refused to accept the truth as Harvey saw it.

Harvey continued to be enterprising throughout his long life. In 1634, his testimony resulted in the pardoning of four convicted "witches." In 1635 he performed necropsy on the body of Thomas Parr, who is said to have lived 152 years. In the early part of the Civil War (1642) a mob attacked his house, stole his goods, and scattered his papers. In 1651 his essay "De Generatione Animalium," a treatise on embryology, was published. He died of a cerebral hemorrhage on June 3, 1657 and was buried in the family vault at Hampstead in Essex.

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Paroxysmal Nonreentrant Tachycardias Due to Simultaneous Conduction in Dual Atrioventricular Nodal Pathways

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Electrophysiologic studies were performed in a 41 year old man for analysis of paroxysmal tachycardias appearing in various electrocardiographic patterns of supraventricular and ventricular bigeminy, junctional and ventricular tachycardia and atrial fibrillation, among others. All these arrhythmias were due to dual atrioventricular (A-V) nodal pathways with simultaneous dual fast and slow conduction of single atrial beats at a normal basic sinus rate. Moderate changes in sinus rate and in fast or slow pathway conduction times, or both, changed the position of the slowly conducted beats between the neighboring two fast conducted beats and resulted in various electrocardiographic manifestations of the conduction disturbance. Different blocks, such as second degree type I, 2:1, 3:1 and possibly also type II, in one of the two pathways and occasionally aberrant conduction induced even more unusual tracings. After intravenous injection of 25 mg of ajmaline, unexpected lengthening and shortening of the A-H interval occurred, suggesting variable shifts between fast and slow pathway conduction.

The incidence of dual A-V nodal pathways is discussed; it was documented in 17 (4.2 percent) of 405 patients studied. A theoretical model of A-V nodal conduction is proposed to explain its normal properties and abnormal patterns.

Conduction studies in several laboratories have shown that atrioventricular (A-V) nodal conduction can longitudinally dissociate into a fast and a slow pathway, causing two different P-R intervals and giving rise to paroxysmal reentrant A-V nodal tachycardias.[1–10] In this paper we analyze the electrophysiologic properties of the fast and slow A-V nodal pathways in a patient who presented runs of *nonreentrant* tachycardias due to dual A-V nodal pathways. In addition, we discuss the incidence of this phenomenon and propose a model for A-V nodal impulse conduction.

Case Report

The patient was a 41 year old man without a history of any serious illness such as scarlet fever, diphtheria or rheumatic fever but a history of moderate ethanol consumption and of a gout attack a year earlier. For the last few years he had paroxysmal pulse irregularities often in connection with emotional stress together with palpitations and sweating. On January 13, 1978 he was admitted to a city hospital for myocardial infarction, but this diagnosis was excluded. There were many rhythm troubles in the form of multifocal ventricular and supraventricular premature beats and short runs of ventricular tachycardia. These rhythm disturbances were resistant to several antiarrhythmic drugs. He therefore was admitted to our center for further evaluation on April 16, 1978. Physical examination as well as chest X-ray films and laboratory data, showed normal findings.

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Electrophysiologic Studies

Three days after discontinuation of administration of cardiac drugs, the patient underwent the first of two electrophysiologic studies: Under fluoroscopic control a tripolar catheter with electrode distances of 10 mm was introduced into the right atrium by way of the right femoral vein and was placed across the tricuspid valve for two His bundle recordings: bipolar leads of the first and second electrodes (HBE_1) and of the second and third electrodes (HBE_2). A quadrupolar electrode catheter with interelectrode distances of 10 mm was introduced by way of the same femoral vein into the high right atrial position for recording and for stimulation. The high right atrial and His bundle electrograms were simultaneously recorded with leads II and V_1 of the surface electrocardiogram on a multichannel system mounted with an ultraviolet (Honeywell) and direct (Hellige) recorder. In addition, recordings were stored on an eight channel tape system to facilitate documentation by replay at the most appropriate paper speed. Measurements were done also on records with a paper speed of 100 mm/sec when they appear at slower speeds in this paper. Pacing was performed by stimuli of two-fold diastolic threshold.

Refractory periods and echo zones were measured with the extrastimulus technique with stimuli delivered after every eighth beat. The coupling interval started at the spontaneous P-P interval and was decreased by 5 to 20 msec increments.

His bundle pacing was performed to validate the His potential according to the method of Narula,[11] and right ventricular pacing for measuring the intervals of retrograde A-V conduction. The conduction intervals were repeatedly determined in the same sequence, first after administration of metoprolol (Lopressor®, Geigy Pharmaceuticals) and subsequently after additional administration of atropine (combined beta adrenergic and parasympathetic blockade, the so-called "intrinsic state"). The electrophysiologic study was repeated after 10 days to test the effect of lidocaine, verapamil and ajmaline on A-V conduction and the arrhythmias.

Special Definitions

The A-V nodal conduction curve is a graphic presentation of the result of programmed stimulation obtained by plotting the A_1–A_2 intervals against the H_1–H_2 intervals. *Dual A-V nodal pathways* are diagnosed when there are spontaneous sudden changes in the P-R interval and the A-V nodal conduction curve is discontinuous at basic cycle lengths. *Latent dual A-V nodal pathways* are suspected when sudden unexpected changes in the H-H interval occur at high frequency atrial stimulation or the A-V nodal conduction curve shows a discontinuity only during programmed stimulation at a driven atrial rate of 100/min or more or after beta adrenergic blockade or in the "intrinsic state," or both.

The Patient's Arrhythmias

In addition to a total of 72 hours of Holter monitoring, numerous electrocardiograms were recorded that were read before the conduction study was performed. These revealed a variety of arrhythmias, including sinus rhythm with supraventricular premature beats and supraventricular bigeminy; sinus rhythm with ventricular bigeminy (Fig. 1A); supraventricular tachycardias (Fig. 1B); atrial fibrillation with ventricular premature beats and occasionally aberrant conduction and intermittent complete A-V block with junctional escape (Fig. 1, C and D); sinus rhythm with second degree A-V block, Mobitz type I and II, and junctional escape beats (Fig. 1E); and sinus rhythm with supraventricular and polymorphic ventricular premature complexes (Fig. 1F). All of these arrhythmias could be observed in the course of the two conduction studies; none of them had mechanisms other than sudden shifts in the dual A-V nodal conduction pathways or simultaneous conduction resulting in double ventricular responses.

Results of The Conduction Study

At a sinus rate of less than 65/min the A′-A (P-A) conduction interval was 30 msec, the A-H interval 120 msec, and the H-V interval 60 msec. At a sinus rate of more than 75/min the A′-A (P-A) and H-V intervals remained unchanged, whereas the A-H interval suddenly increased to 440 msec. In the range between these two rates a spontaneous sudden prolongation and shortening of the A-H interval was repeatedly observed (Fig. 2). Sometimes longer Wenckebach periods occurred in the fast pathway before the slow pathway took over. On other occasions the shift took place without prior A-H and P-R interval prolongation, suggesting a type II block in the fast pathway conduction. The change from slow to fast pathway conduction was mostly preceded by moderate shortening of slow pathway conduction (see also Fig. 6).

During the course of programmed atrial stimulation a sudden prolongation of the H_1–H_2 and A_2–H_2 intervals appeared at a prematurity of 830 msec. When the prematurity was increased to 760 msec two groups of H_1–H_2 responses were recorded: One was consistent with the usual A-V nodal (fast pathway) conduction (circles in Fig. 3) and the other with slow pathway conduction, showing a significant prolongation of the A_2–H_2 interval (squares in Fig. 3). A further increase of prematurity resulted in pure slow pathway conduction until A-V conduction ceased at 540 msec, that is, the fast pathway effective refractory period was 760 msec, and the slow pathway effective refractory period 560 msec, with an overlapping period of 830 to 760 msec.

Simultaneous fast and slow pathway conduction appearing occasionally, created the picture of premature supraventricular complexes, and, if conducted aberrantly, premature ventricular complexes. Longer unbroken periods of combined fast and slow conduction resulted in supraventricular or ventricular bigeminy (Fig. 1A and 4). When the slow pathway conduction time divided the sinus cycle length into two halves (Fig. 5) and the P waves were hidden in the T waves of the slowly conducted ventricular beats, the typical picture of a junctional tachycardia occurred in the surface electrocardiogram (Fig. 1B).

Permanent slow pathway conduction with periodic block (2:1, 3:1, and so forth) in the fast conduction pathway imitated a junctional rhythm with premature complexes or even atrial fibrillation with premature ventricular complexes and occasionally aberrant conduction (Fig. 1, C and D, and 6).

Effects of drugs on rate and rhythm: After beta adrenergic blockade with a single intravenous dose of 10 mg of metoprolol the sinus rate slowed from 72 to 62 beats/min. The fast pathway effective refractory period increased to 860 msec and the slow pathway effective refractory period to 740 msec, with an overlapping period of 900 to 860 msec. Additional intravenous administration of 2 mg of atropine (intrinsic heart state) decreased the fast and slow pathway effective refractory periods to 680 and 670 msec, respectively, with an overlapping period of 715 to 680 msec. The sinus rate reaccelerated to 78 beats/min.

Lidocaine given in a single intravenous dose of 150 mg did not result in any changes in conduction or in arrhythmias. With a single intravenous dose of 5 mg of verapamil the fast and slow pathway refractory periods increased to 810 msec

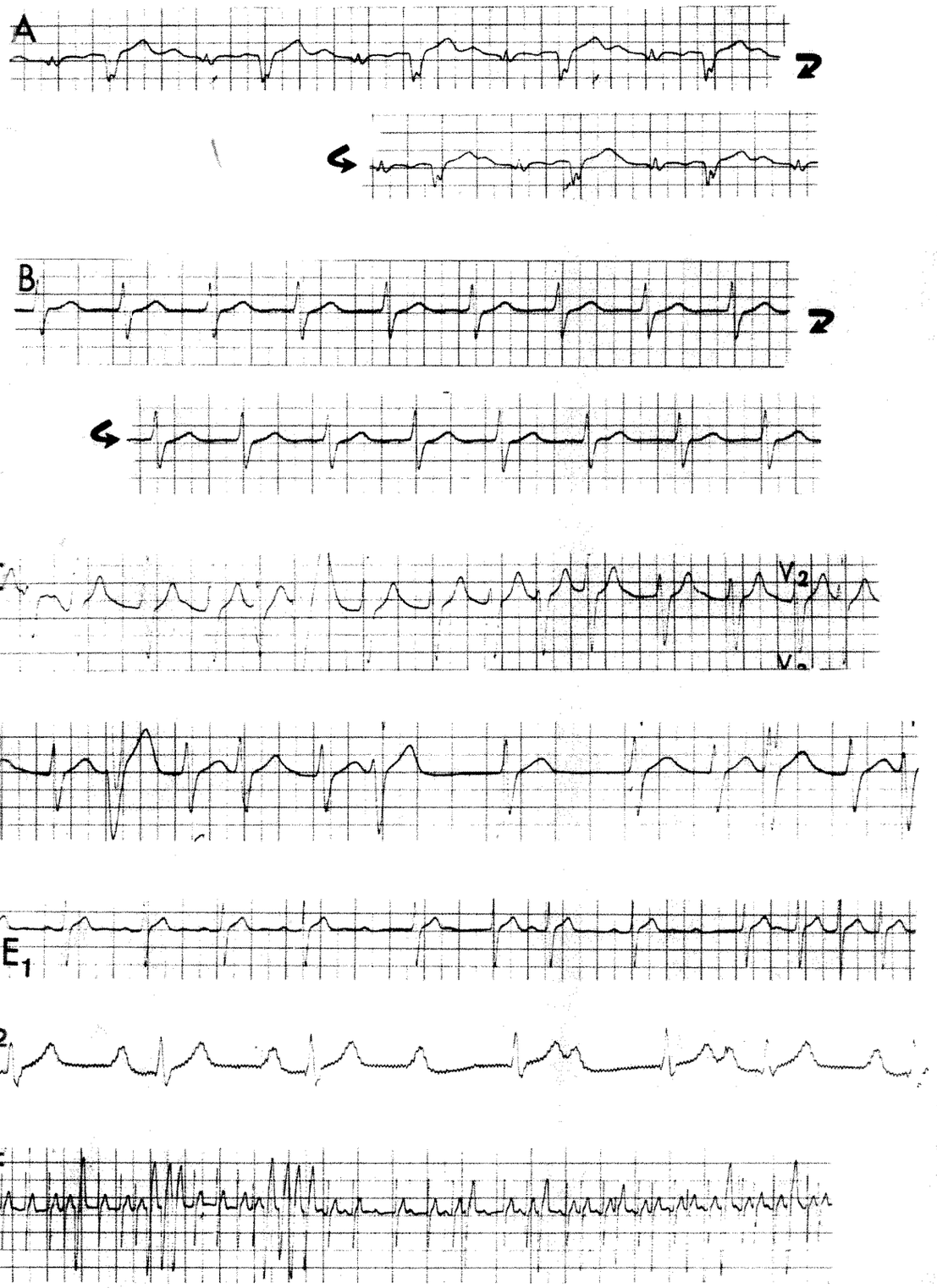


FIGURE 1. Electrocardiograms and rhythm strips taken before the conduction study and interpreted as follows: **A,** normal sinus rhythm with ventricular bigeminy; **B,** junctional tachycardia; **C,** atrial fibrillation with occasionally aberrant conduction; **D,** atrial fibrillation with intermittent complete A-V block and junctional escape; **E,** sinus rhythm with second degree block, types I and II, and junctional escape; and **F,** sinus rhythm with supraventricular and ventricular premature beats, second degree type I block, concealed conduction and short runs of ventricular tachycardia, with occasional junctional rhythm. Paper speed 50 mm/sec (**A** to **D** and E_2), 25 mm/sec (E_1), and 10 mm/sec (**F**).

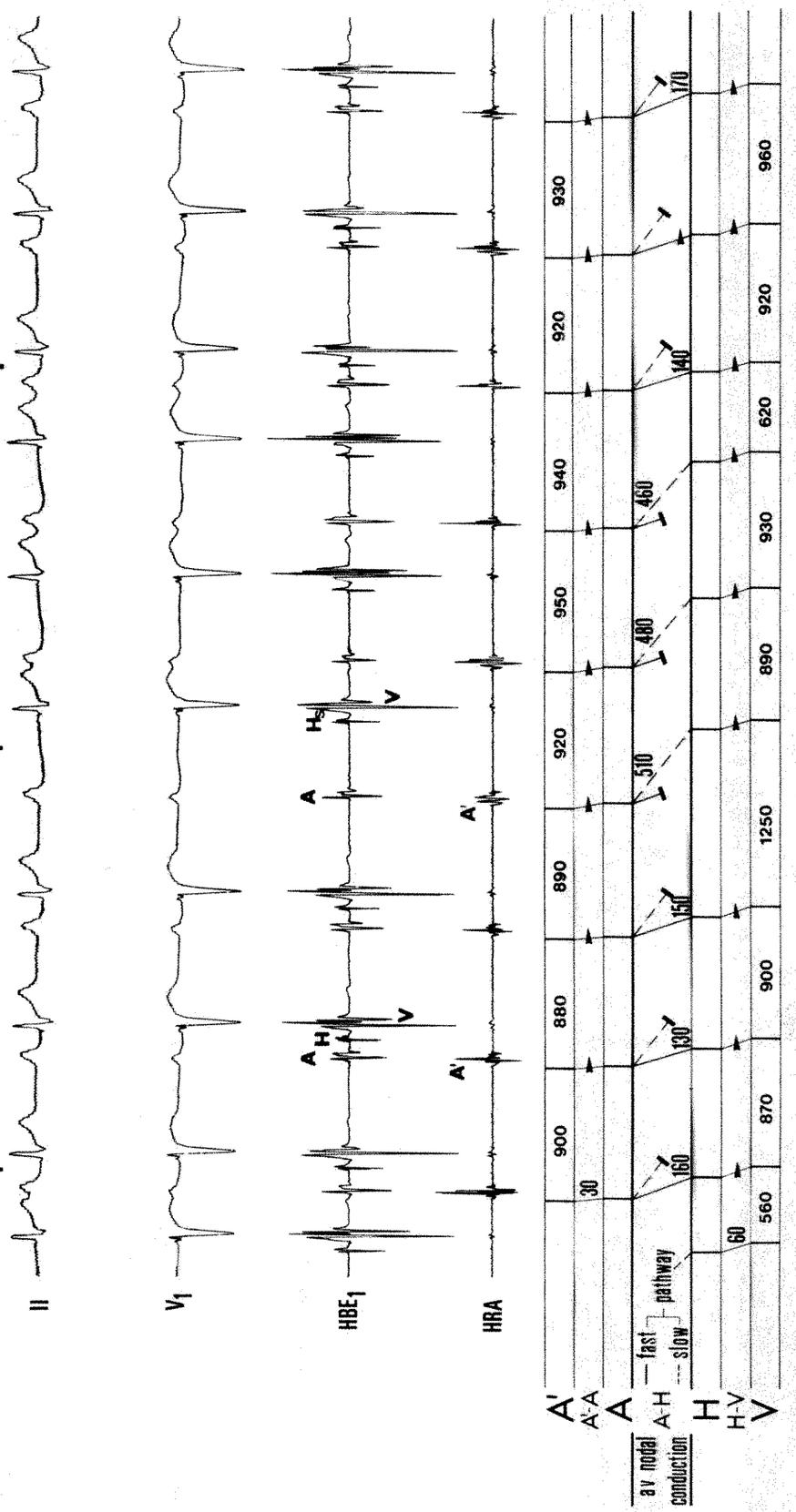


FIGURE 2. Spontaneous shift of A-V nodal conduction from the fast to the slow pathway (fourth beat) and vice versa (seventh beat). Note the moderate increase in fast pathway conduction preceding the takeover of slow conduction, indicating a second degree type I block in the fast pathway. A progressive decrease of the A-H interval appears before fast conduction returns, suggesting either a concealed conduction phenomenon in the slow pathway or increasing partial participation of fast channels throughout A-V nodal conduction. Paper speed 50 mm/sec. AV = atrioventricular; HBE_1 = His bundle electrogram; HRA = high atrial electrogram; H_S = His bundle deflection due to slow pathway conduction.

and 690 msec, respectively, and the overlapping period disappeared. First degree block within the His bundle was indicated by a prolonged H-V interval with a normal QRS complex. Under the influence of verapamil split His and higher degree His bundle block occurred in the slow conducted beats if these were preceded by fast conduction of the same atrial beat (Fig. 5).

After intravenous administration of 25 mg of ajmaline A-V nodal conduction became chaotic; in addition to fast, slow and simultaneous dual conduction, unexpected lengthening and shortening of A-V nodal conduction occurred, with A-H intervals ranging from the fast to the slow conduction time seen previously (Fig. 7). These changes also made it impossible to plot the A-V nodal conduction curve.

Discussion

Longitudinal dissociation of A-V nodal conduction was demonstrated in the animal experiments of Moe et al.[1] and Rosenbluth and Rubio[2]: The existence of two A-V nodal pathways with different electrophysiologic properties had to be assumed to explain the echo beats occurring after premature atrial or ventricular stimulation at a critical interval. Mendez et al.,[3] studying the characteristics of ventricular echoes by direct His bundle stimulation, found the phenomena often enough to propose that longitudinal dissociation can be incited in the normal A-V node and is not an unusual pathologic pattern. As early as 1943, Barker et al.[12] postulated a reciprocation of echoes through the A-V node in explaining the mechanism of A-V nodal tachycardia.

A-V nodal reentry and rate of longitudinal A-V nodal dissociation: Mendez et al.[3] defined the necessary conduction criteria for the repetition of the echo phenomenon (that is, for the development of a reentry circuit), as follows: (1) The round trip conduction time must exceed the refractory period, and (2) lateral propagation (short circuit) of the circling impulse must be impossible. Rosen et al.[7] demonstrated dual A-V nodal pathways in an electrophysiologic study in a patient with two different P-R intervals during atrial stimulation. They also proved the principal role of longitudinal A-V nodal dissociation in the genesis of some cases of tachycardia and described the discontinuity of the A-V nodal conduction curve as a typical electrophysiologic manifestation of dual A-V nodal pathways.[7-9,13-21] Since this first observation in human subjects,[7] other investigators[22,23] have successfully demonstrated dual A-V nodal pathways in patients with reentrant tachycardias as well as in patients with no tachycardia.

Incidence of dual A-V nodal pathways: The real incidence of this pattern cannot yet be determined, because newly realized manifestations of longitudinal dissociation[24] as well as provocative methods for demonstrating dual A-V nodal pathways—premature stimulation during a high driving atrial rate[14] or conduction studies after beta adrenergic blockade[25]—have only begun to be described.

Rosen et al.[17] disclosed patterns of dual A-V nodal pathways in 41 (10.3 percent) of their 397 patients studied with atrial extrastimulus techniques; 17 (41 percent) of these 41 patients had had documented paroxysmal supraventricular tachycardias. Bisset et al.[23] demonstrated dual A-V nodal pathways in 7 of 13 patients with paroxysmal supraventricular tachycardia and in 9 of 135 patients without tachycardia. Dual responses of A-V nodal conduction were observed by Ingham et al.[25] in 7 of 13 patients with idiopathic hypertrophic subaortic stenosis. In 7 of the 10 patients with paroxysmal supraventricular tachycardia described by Wellens et al.,[26] a sudden increase of the A-H interval in the beat triggering the tachycardia suggested the existence of dual A-V nodal pathways. In their study to estimate the incidence of dual pathways, Nava et al.[27] plotted discontinuous A-V nodal conduction curves in 25 of 28 patients with rhythm disturbances.

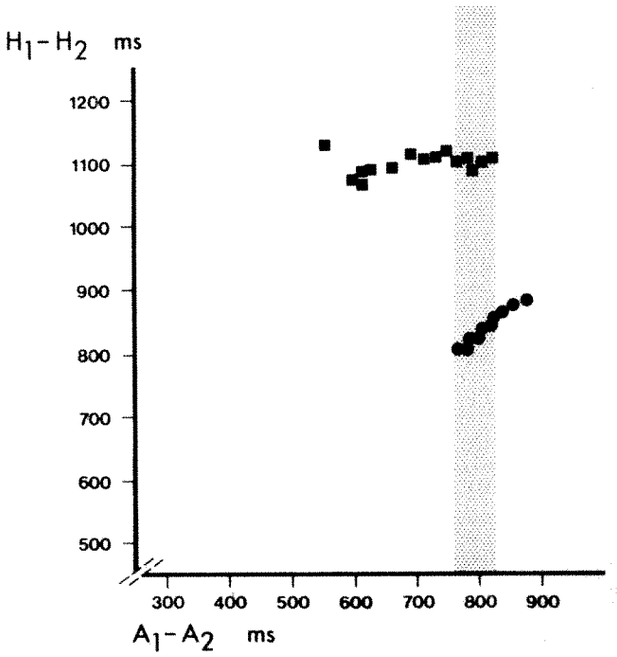


FIGURE 3. A-V nodal conduction curve (A_1–A_2 intervals plotted against H_1–H_2 intervals) during basic sinus rate. **Closed circles** = fast pathway conduction and **closed squares** = slow pathway conduction after stimulation at basic fast pathway conduction. ms = milliseconds.

We found 17 cases (4.2 percent) of longitudinal dissociation of A-V nodal conduction (10 dual A-V nodal pathways and 7 latent dual A-V nodal pathways) among the 405 patients who underwent conduction studies in our laboratory. Twelve of these 17 patients had paroxysmal supraventricular reentrant tachycardias, representing 7.1 percent of the 168 patients studied for paroxysmal tachycardias. Our cases surely do not represent the real incidence of longitudinal A-V nodal dissociation, because special efforts to disclose this conduction disorder have been made only in the last few months in our laboratory.

Electrophysiologic mechanisms: The increasing rate of recognition of longitudinal A-V nodal dissociation has led many investigators[3,14,22,27] to consider this

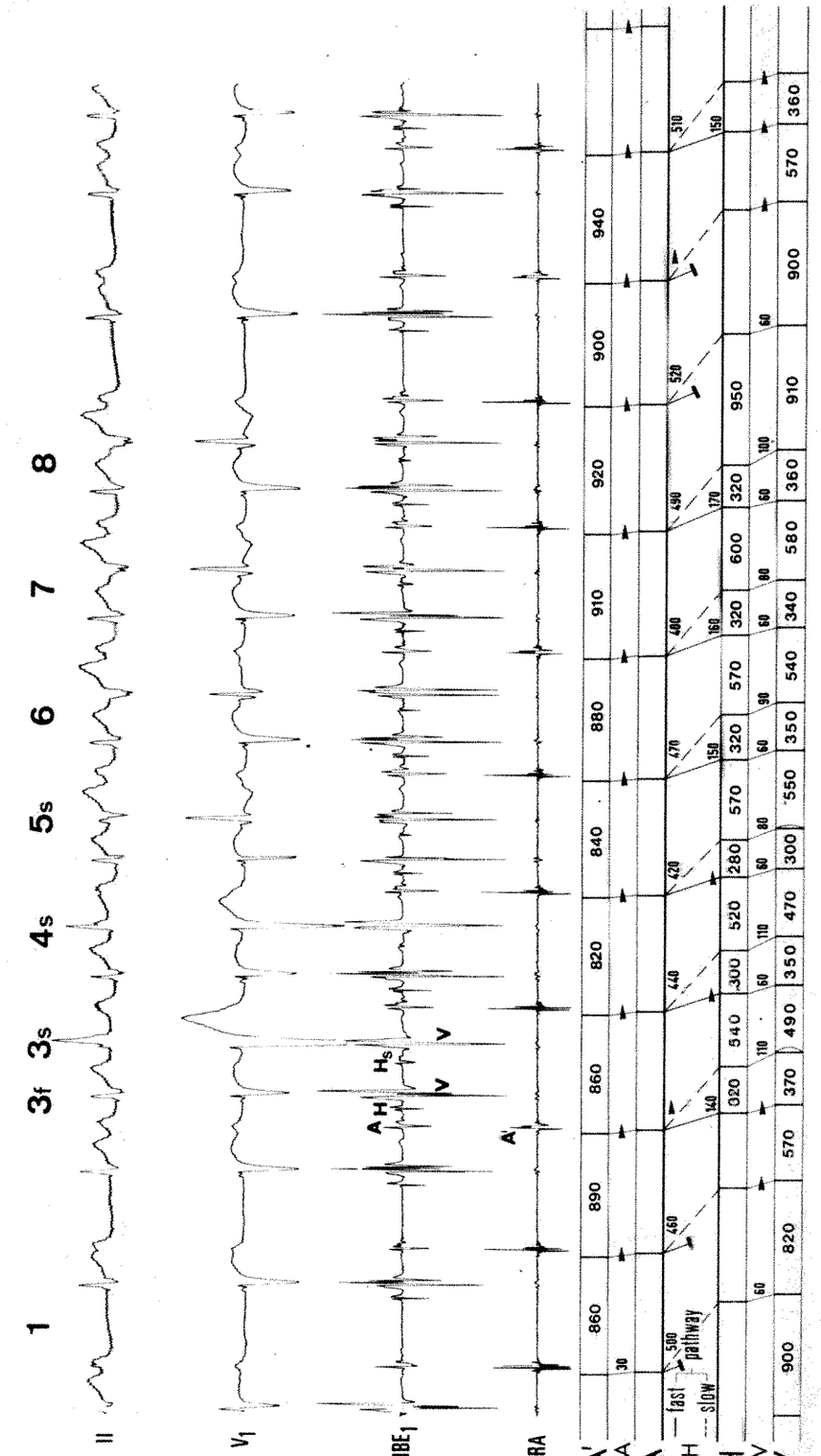


FIGURE 4. Intracardiac tracing with electrocardiogram comparable with that of Figure 1A. Simultaneous fast and slow pathway conduction starts in the third atrial beat. The slow component of the third beat (3s) imitates a ventricular premature beat, and that of 4s and 5s a supraventricular premature beat with aberrant conduction. The electrocardiographic appearance of the sixth, seventh and eighth beats is similar to that of ventricular bigeminy and could be correctly interpreted only with His bundle recording. Paper speed 50 mm/sec. Abbreviations as in Figure 2.

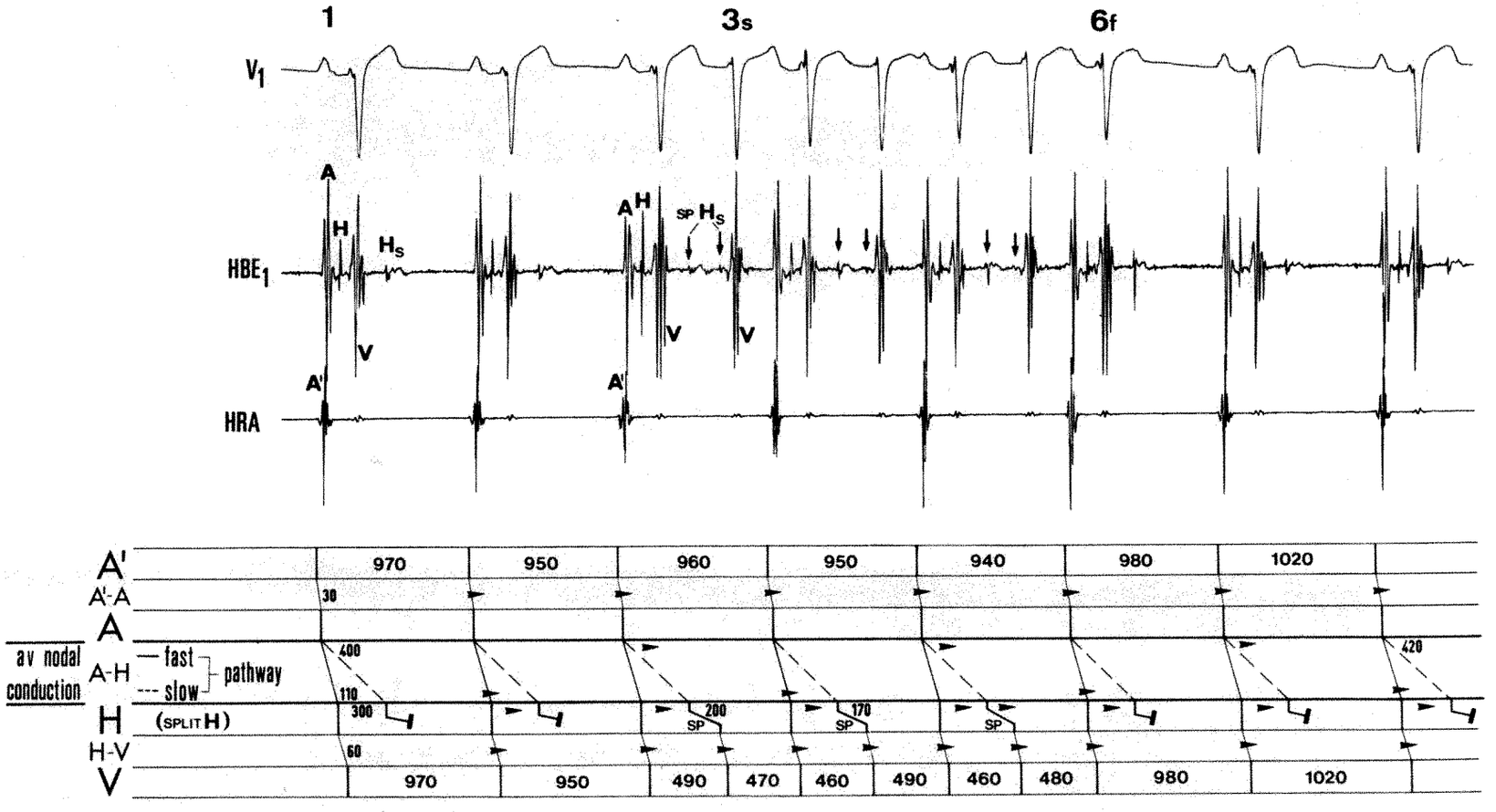


FIGURE 5. Simultaneous dual A-V nodal conduction resulting in a twofold ventricular rate during paroxysmal tachycardia and imitating a junctional tachycardia with A-V nodal dissociation starting from the slow component of the third beat (3s) up to the fast component of the sixth beat (6f). Paper speed 50 mm/sec; sp (in the ladder diagram) and spH (in the tracing) = split His deflection; other abbreviations as in Figure 2.

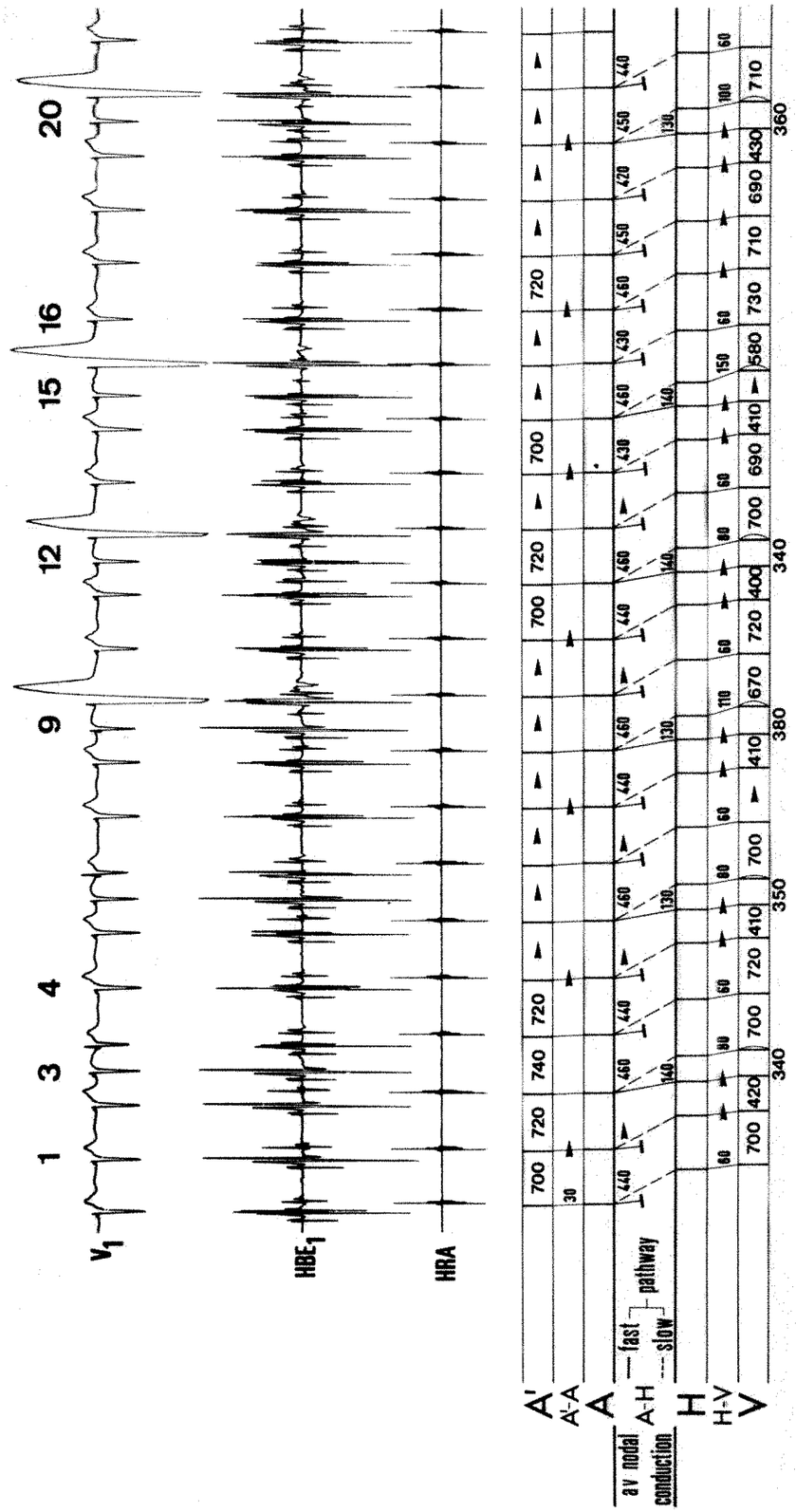


FIGURE 6. Basic slow pathway conduction with 3:1 block (from the 4th to the 15th beats) and 5:1 block (16th to 20th beats) in fast pathway conduction. After fast pathway conduction an increase of 20 to 30 msec occurs in slow pathway conduction (3rd, 9th, 12th, 15th and 20th beats), suggesting a partial slow pathway depolarization during fast conduction. In these slowly conducted beats H-V interval prolongation and aberrant conduction occur. The surface electrocardiographic features of this arrhythmia resembles those of a junctional rhythm with ventricular premature complexes and atrial fibrillation with aberrantly conducted complexes, respectively (companion to Fig. 1C). Paper speed 25 mm/sec. Abbreviations as in Figure 2.

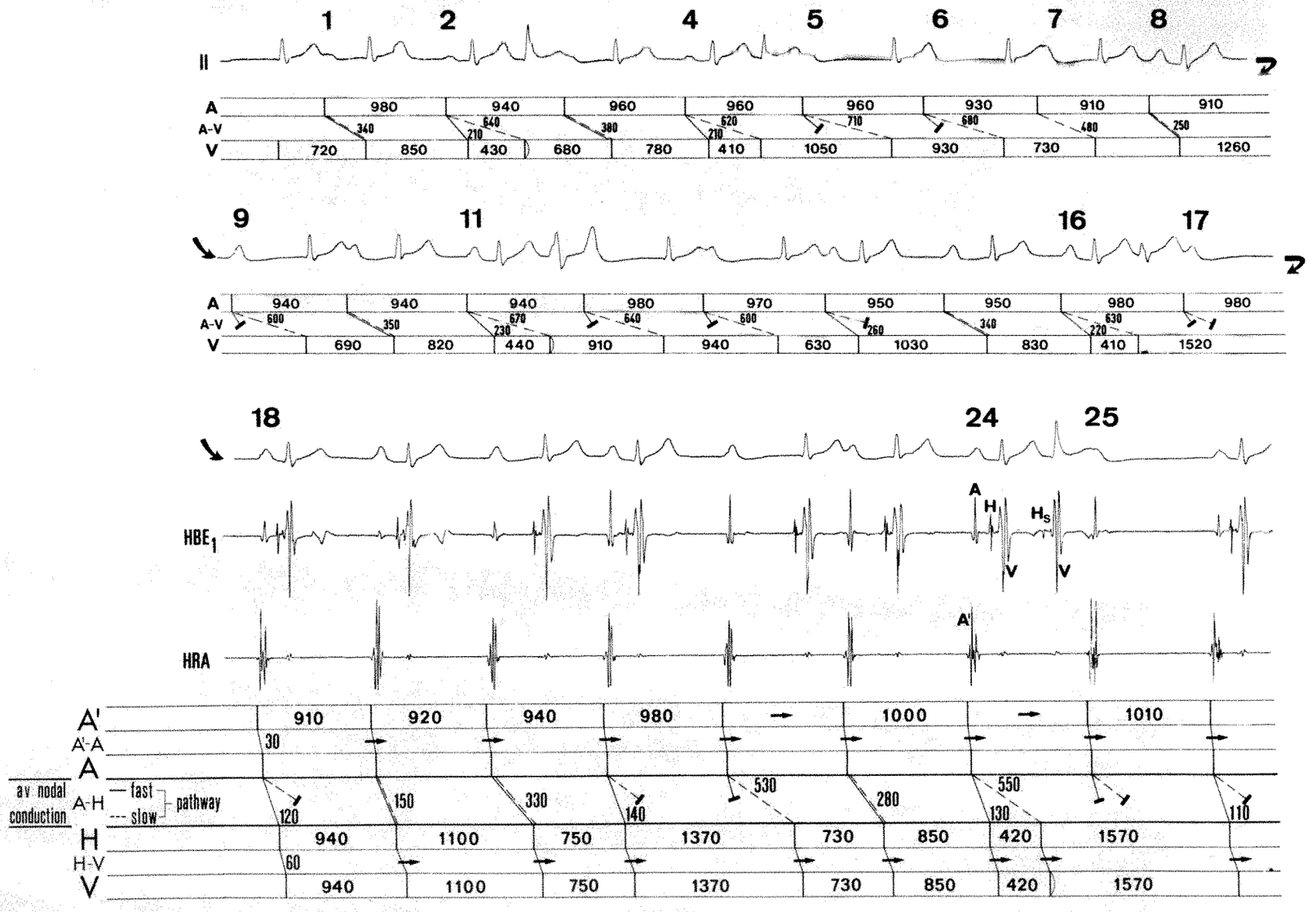


FIGURE 7. Continuously changing P-R intervals after administration of ajmaline are suggestive of combined fast and slow conduction with occasionally simultaneous dual conduction (2nd, 4th, 11th, 16th and 24th beats) and with simultaneous block in both pathways (17th and 25th beats). Paper speed 50 mm/sec. Abbreviations as in Figure 2.

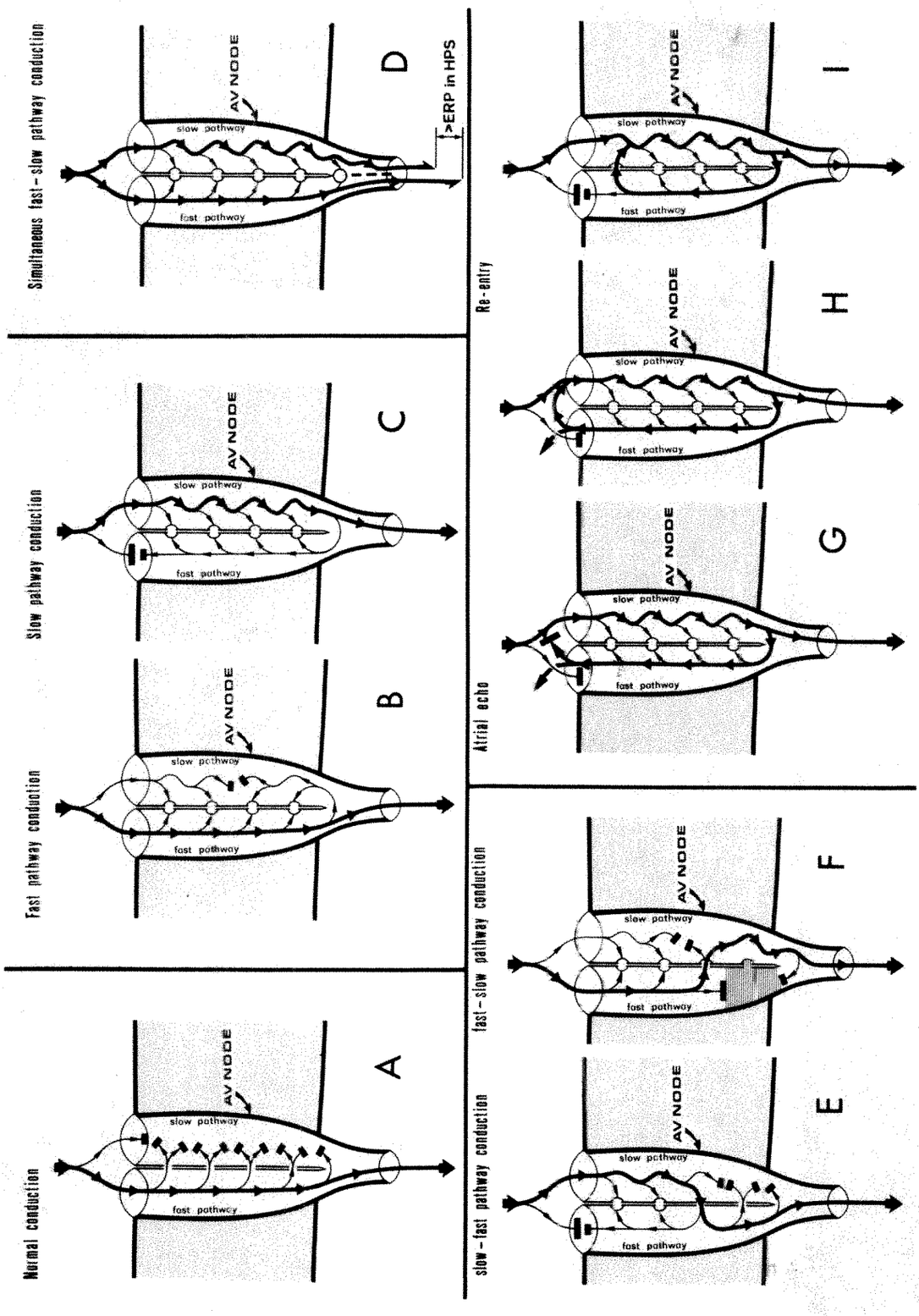


FIGURE 8. Schematic presentation of normal A-V conduction (**A**); fast pathway conduction (**B**); slow pathway conduction with anterograde block and retrograde impulse progagation in the fast pathway (**C**); combined simultaneous fast and slow conduction with lateral block between the two pathways (**D**); combined slow and fast conduction (**E**); fast and slow conduction (**F**); mechanism of an atrial echo (**G**); I, mechanism of A-V nodal reentry linking the circuit in the atrium (**H**) and within the A-V node (**I**). ERP in HPS = effective refractory period in His-Purkinje system.

pattern a pathologic alteration of a normal phenomenon rather than a pathologic conduction variant. This alteration is likely to be caused by an advanced shift in the refractory periods of the A-V nodal conduction fibers or by an increasing block in lateral impulse propagation, or both. If the dissociation occurs in the upper part of the A-V node and the lateral block is complete within the node, as proposed by Moe et al.[1] and Mendez et al.,[3] the atrium is a necessary link for A-V nodal reentry (Fig. 8H). This can easily explain why atrial fibrillation due to overdrive stimulation converts to sinus rhythm instead of returning to the tachycardia. If lateral conduction can occur within the A-V node, the atrium is not necessary for the echo pathway (Fig. 8I), as demonstrated in two cases described by Schuilenburg and Durrer[28] and in one patient described by Wu et al.[29]

Dual pathways between the atria and ventricles frequently create the anatomic basis for reentrant tachycardias, one pathway serving the anterograde and the other the retrograde conduction within the reentry circuit. Double capture of the ventricle by a single atrial impulse is theoretically also possible when in one of the two pathways the impulse is conducted slowly enough to reach the ventricle only after recovery from the contraction caused by the prior conduction. Grolleau et al.[30] and Guize et al.[31] demonstrated double ventricular activations from a single atrial beat in the Wolff-Parkinson-White-syndrome, and Motté et al.[32] observed the same phenomenon in the presence of a James bundle. In addition, Bailey et al.[33] documented double responses of a single stimulus in cases of longitudinal dissociation within the His-Purkinje system in animal experiments. Wu et al.[9,29] documented dual conduction of a stimulated atrial beat in two patients with dual A-V nodal pathways during atrial stimulation at rates sufficient to produce Wenckebach block.

Mechanisms of arrhythmias in reported case: In our case the effective refractory period of the His-Purkinje system was shorter than the difference between fast and slow pathway conduction times (Fig. 8D). It thus became possible for single atrial beats to initiate two ventricular responses, thereby causing tachycardias with a twofold sinus rate appearing in paroxysm and lasting from a few beats to more than 3 hours. Small changes in sinus rate and in the speed of the fast and slow pathway conduction resulted in changes in the position of the slowly conducted beats between two fast ones and in the coupling intervals of the slowly conducted beats. Changes of this kind were easy to reproduce during the conduction study by administering a beta adrenergic blocking agent and atropine. Different blocks, such as second degree type I, 2:1, 3:1, possibly also second degree type II, in one of the dual pathways produced arrhythmias that could not be interpreted correctly by means of the surface electrocardiogram and imitated junctional rhythm with premature complexes or sometimes even paroxysmal atrial fibrillation. In addition to these conduction defects, frequent aberrant ventricular conduction occurred. Intermittent widening and alteration in the QRS configuration made the

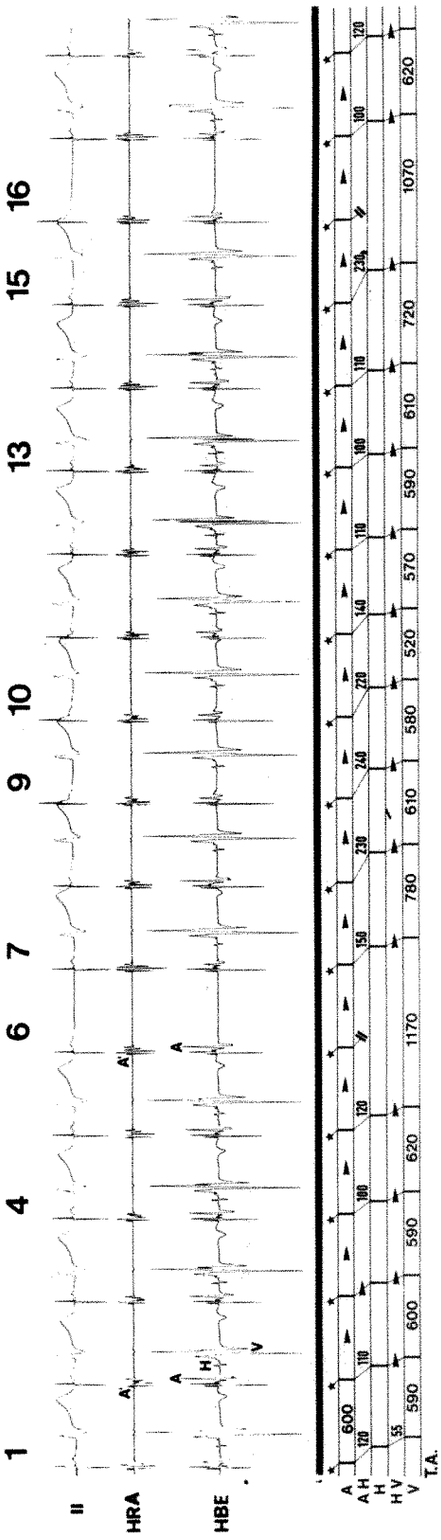


FIGURE 9: Accelerated atrial stimulation at a rate of 10/min in another 24 year old woman with dual A-V nodal pathways. Before the first dropped beat (beat 6) a slight increase in the A-H interval is preceded by a slight decrease in the A-H interval (from the first to the fourth beats). A progressive increase in the A-H interval in the 7th to the 9th beats is followed by a progressive decrease in this interval (from the 10th to the 13th beats). Thereafter a sudden increase and block in A-V nodal conduction occurs (15th and 16th beats). Paper speed 50 mm/sec. Abbreviations as in Figure 2.

electrocardiographic records of rhythm disturbances even more unusual. These arrhythmias could be distinguished from ventricular premature beats, ventricular bigeminy and short runs of ventricular tachycardias only by intracardial tracings.

Our observation of the A-V nodal conduction after administration of ajmaline deserves particular attention (Fig. 2). Unexpected shortening and lengthening in A-V conduction of singly conducted beats occurred, resulting in variable P-R intervals ranging from 210 msec (as in the 18th beat) to 710 msec (as in the 5th beat). The same changes in A-V nodal conduction could be observed in two additional patients with dual A-V nodal pathways during accelerated atrial stimulation (Fig. 9).

Proposed model of A-V conduction: In postulating a failure of lateral impulse propagation, one has to consider the presence of more anatomically defined conducting channels within the A-V node to explain such changes in the P-R interval, although this possibility seems highly improbable. It is more likely that functional preferential pathways develop by crossing the impulse from one to the other pathway at different sites of the A-V node (Fig. 8, E and F), as also proposed by Roworth et al.[10] Because in our case the effective refractory period of the fast pathway was longer than that of the slow pathway, it seems evident that the atrial impulse entered the A-V node by way of the slow pathway and at a point where the fast pathway recovery overtook its slow penetration; in other words, at the point where the fast pathway became free for conduction the impulse shifted from the slow to the fast pathway (Fig. 8E). The higher this shift takes place, the faster the entire A-V conduction.

In this model the normal A-V conduction could be explained as follows: The impulse penetrated through the fast pathway, continuously stimulating the slow pathway through cross-connections (Fig. 8A); the slow pathway was thereby switched off from the normal conduction, but it assumed its role in conduction when the fast pathway recovery time exceeded the supraventricular cycle length. This could also explain why Denes et al.[14] found greater incidence of discontinuous A-V nodal conduction curves when the heart was driven near the rate at which Wenckebach block occurs than during spontaneous sinus rhythm. A shift from the slow to the fast pathway at a progressively more distal point or from the fast to the slow pathway at an increasingly more proximal point could also explain the characteristics of the type I (Wenckebach) second degree block.

It is the basic property of any current to take the fastest and shortest possible route to its destination. On the basis of this rule, changing the switching point back and forth with possible detours might be one explanation of the continuously varying A-V conduction seen regularly in atrial fibrillation and in our patient also during normal sinus rhythm after administration of ajmaline. The electrophysiologic pattern known as double A-V nodal pathway would then be caused by failure in lateral impulse conduction on a functional or anatomic basis, or by increased differences in the refractory periods of the fast and slow conducting A-V nodal fibers, or both (Fig. 8, B to D and G to I).

Implications: On the basis of their observations, Wu et al.[29] expected that double conduction of a single atrial beat could play an important role in the genesis of some premature superventricular beats and bigeminy. Our case strengthens this hypothesis and presents the ability of this conduction defect to imitate other kinds of arrhythmias as well. On the basis of previous reports and our observations on bidirectional changes of the A-H interval, a hypothetical model of A-V nodal conduction was composed. Further clinical and experimental studies are required to disclose the incidence of arrhythmias due to simultaneous fast and slow conduction in the presence of dual A-V nodal pathways and to prove or disprove the validity of the conduction model presented here.

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Systolic Click From a Swan-Ganz Catheter: Phonoechocardiographic Depiction of the Underlying Mechanism

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Although echocardiographic manifestations of Swan-Ganz catheters have received increasing attention, auscultatory sequelae have not previously been described. In the patient described in this report, insertion of a Swan-Ganz catheter resulted in a loud mid systolic click; removal of the catheter eliminated the click. Simultaneous phonoechocardiograms suggest that the click resulted from crisp contact of the catheter against the ventricular septum. Catheter momentum was enhanced by wide excursion and systemic pressures in the right ventricle; paradoxical motion of the septum during systole may have accentuated the force of its contact with the catheter.

The manner in which Swan-Ganz balloon flotation catheters may mimic the echocardiographic appearance of normal or abnormal cardiac structures has recently been outlined.[1,2] However, no previous reports have described sounds produced by these catheters that simulated normal or abnormal auscultatory events. We report here a patient in whom a Swan-Ganz catheter produced a mid systolic click, indistinguishable from that considered classic for atrioventricular valve prolapse.

Case Summary

A 54 year old woman was referred to Georgetown University Hospital for evaluation of primary pulmonary hypertension. Precordial examination on admission disclosed a normal first heart sound; the second sound was physiologically split with a markedly accentuated pulmonary component. A grade 3/6 holosystolic murmur was heard best at the fourth interspace adjacent to the left sternal border; the murmur increased a full grade with inspiration. A third sound that increased with inspiration was heard at the same location. No systolic clicks were heard. The electrocardiogram was consistent with right ventricular hypertrophy.

At cardiac catheterization the pressures (in mm Hg) were: mean right atrium 20, right ventricle 120/25, pulmonary artery 120/75, mean pulmonary capillary wedge 8 and brachial artery 135/75. Selective pulmonary arteriograms were consistent with primary pulmonary hypertension.

On completion of the catheterization, a no. 7 Swan-Ganz thermodilution balloon flotation catheter was positioned in the main right pulmonary artery. Auscultation shortly thereafter disclosed a mid systolic click in addition to the previously described systolic murmur. Simultaneous phonocardiogram and echocardiogram performed at this time documented a mid systolic click that corresponded temporally to the abrupt termination of the phasic motion of the Swan-Ganz catheter (Fig. 1). The click persisted over the next 3 days, but on the 4th day it was not heard. An echocardiogram done at this time showed that the wide phasic catheter motion seen in the previous study was no longer present (Fig. 2). However, phonoechocardiography performed as the catheter was being slowly withdrawn demonstrated the simultaneous reappearance of both the systolic click and the phasic catheter motion (Fig. 3). Withdrawal of the catheter from the right ventricle resulted in simultaneous phonocardiographic disappearance of the systolic click and echocardiographic disappearance of the catheter motion. The echocardiographic motion of the tricuspid valve was normal. The echocardiographic pattern of mitral and tricuspid valve motion never suggested prolapse of either valve. No systolic click was detected on numerous follow-up examinations during the next 12 months.

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Discussion

A mid systolic click is generally regarded as a fairly specific and sensitive manifestation of organic heart disease. Idiopathic focal hooding of the mitral or tricuspid valve resulting in systolic prolapse of one or more than one leaflet is by far the most common underlying basis,[3] although other causes have been suggested.[4–7] Iatrogenic clicks, on the other hand, are uncommon, but have been observed in association with transvenous pacemakers.[8] These pacemaker-induced clicks are most often *pre*systolic events, and have been shown to occur as a result of pacemaker stimulation of intercostal muscle contraction.[9–11]

Nachnani et al.,[12] however, described three patients in whom a click associated with a temporary transvenous pacemaker catheter was heard during systole. In addition, each of these patients had a "scratchy, superficial" systolic murmur that was localized to the fourth and fifth interspace at the left sternal border and became louder on inspiration. Both the click and murmur disappeared on removal of the catheter. The authors postulated that the murmur represented tricuspid insufficiency caused by mechanical interference with tricuspid valve closure. They further proposed that the click occurred as the result of a catheter-induced deformity of the tricuspid chordae tendineae "as their tension is abruptly altered during ventricular systole" in a manner similar to that proposed by Reid[13] as the origin of the click in mitral valve prolapse. No echocardiographic demonstration of the motion of the catheter or the mitral or tricuspid valve was presented.

In our patient, the temporal correspondence between the auscultatory and echocardiographic findings and sequence of catheter insertion, repositioning and removal clearly demonstrate that the click was produced by the Swan-Ganz catheter. The series of phonocardiograms and echocardiograms suggest that the click was produced by the catheter slapping against the ventricular septum. Figures 1 and 3 demonstrate that the click occurred simultaneously with abrupt termination of the wide phasic motion of the Swan-Ganz catheter. Figure 3 shows a slight but definite beat to beat variation in the interval between S_1 and the click. However, in each cycle, timing of the click corresponds precisely to abrupt termination (by the ventricular septum) of the phasic catheter motion. The timing of the systolic click thus varies according to the timing of catheter-septum contact, additional evidence that this catheter-septum contact is generating the click.

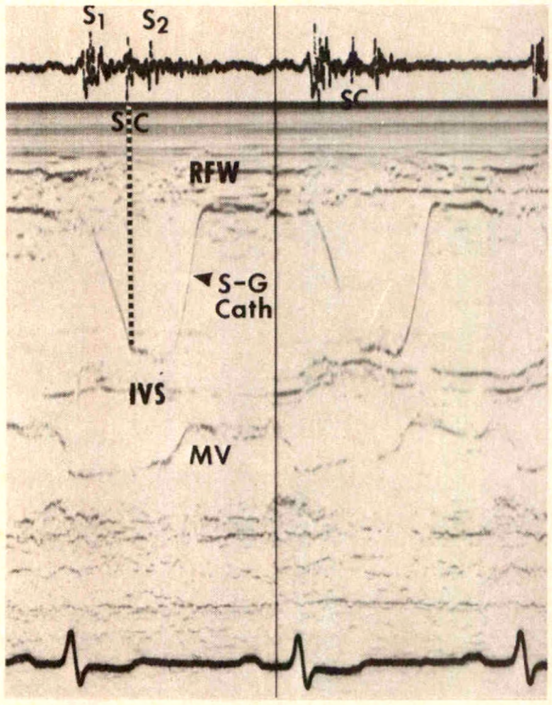


FIGURE 1. Echoes from the Swan-Ganz catheter (S-G Cath) are recorded within the right ventricular cavity. Wide phasic motion of the catheter is seen. The systolic click (SC) in the phonocardiogram occurs at the point of maximal posterior excursion of the catheter. IVS = interventricular septum; MV = mitral valve; RFW = right ventricular free wall; S_1 and S_2 = first and second heart sounds, respectively; Time lines = 1 second.

Factors producing the systolic click: Bedside hemodynamic monitoring with balloon flotation catheters has become a widely employed technique. Yet despite

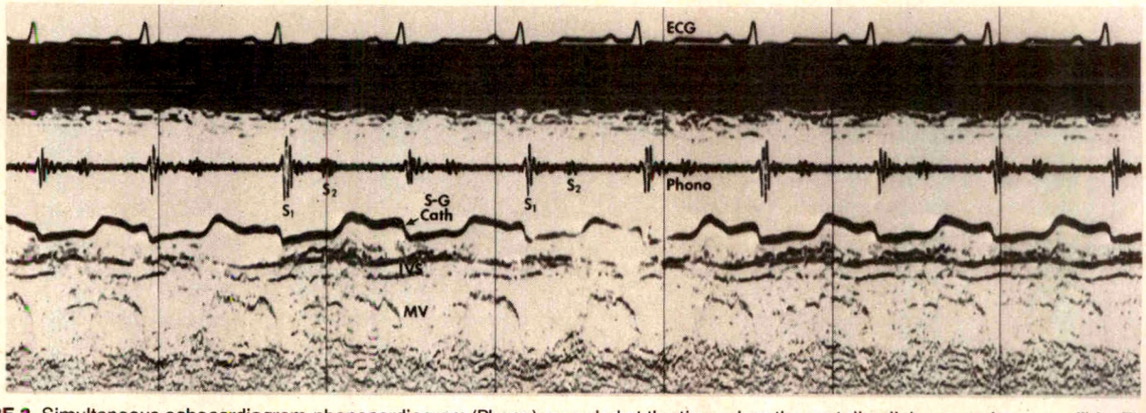


FIGURE 2. Simultaneous echocardiogram-phonocardiogram (Phono) recorded at the time when the systolic click was no longer audible. The wide catheter (S-G Cath) excursion demonstrated previously is no longer seen. ECG = electrocardiogram; IVS = interventricular septum; MV = mitral valve.

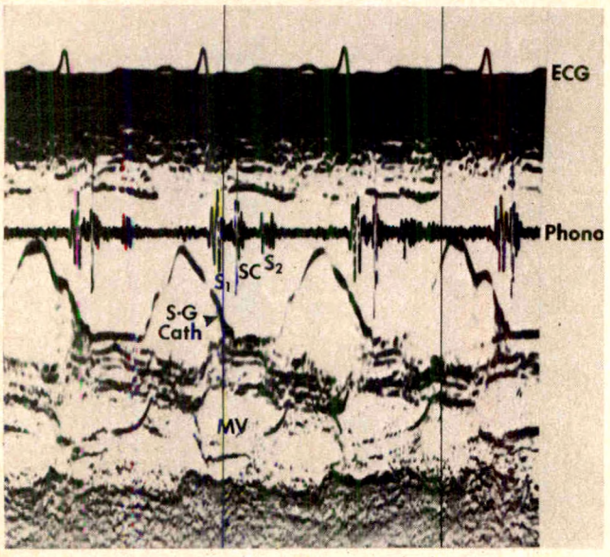


FIGURE 3. Simultaneous echocardiogram-phonocardiogram performed after repositioning of the Swan-Ganz catheter (S-G Cath). The recording demonstrates the reappearance of both the wide catheter excursion and the systolic click (SC). The posteriormost displacement of the catheter is again seen to coincide with the click. ECG = electrocardiogram; MV = mitral valve; Phono = phonocardiogram; S_1 and S_2 = first and second heart sounds, respectively.

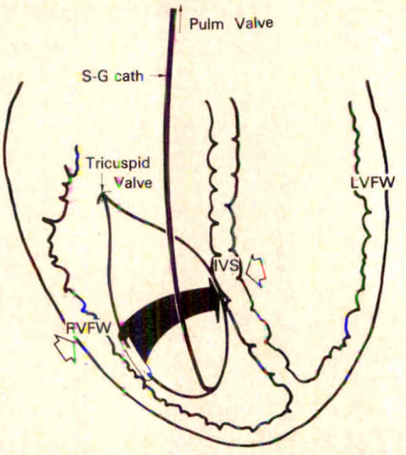


FIGURE 4. Schematic diagram illustrating production of systolic click by Swan-Ganz catheter (S-G cath). During diastole, the catheter rests against the right ventricular free wall (RVFW). With the onset of systole **(white arrows)**, the inflow portion of the catheter pivots on the fixed outflow portion of the catheter and sweeps across the right ventricle **(black arrow)**, contacting the ventricular septum (IVS). Generation of systemic pressure by the right ventricle during systole accelerates the sweep of the catheter across the ventricle. Paradoxical movement of the septum abruptly terminates the catheter sweep, yielding heightened impact on contact with septum. LVFW = left ventricular free wall; Pulm = pulmonary.

the frequency with which this procedure is employed, catheter-induced clicks are apparently rare. Why a rare auscultatory abnormality resulted in our patient may be related to three factors (Fig. 4). The first is the momentum associated with the wide catheter excursion. Catheter excursion was observed to be diminished when the click was not audible (Fig. 2). When the catheter began its sweep at a greater distance from the septum (Fig. 1 and 3), the heightened impact generated a sound. The circumstance is analogous to striking a whip against a flat surface; increasing the wind-up results in an amplified impact when the whip contacts the surface.

Second, the systemic pressure generated by the right ventricle may have accelerated the catheter in its sweep across the ventricle, slamming the catheter into the septum with even greater momentum. Although wide catheter excursion has previously been demonstrated with echocardiography,[1,2] we are not aware of any reports describing such wide catheter excursion in combination with right-sided systolic pressures in excess of 100 mm Hg.

Finally, Figures 1 to 3 all show frankly paradoxical motion of the ventricular septum. This persisted in the echocardiograms recorded from the septum below the tips of the mitral valve and was presumably related to right ventricular overload in this patient. It is possible that the fortuitous combination of rapid posterior catheter motion and rapid anterior septal motion was the critical factor that allowed catheter-septum contact and the resultant systolic click.

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Mid Systolic Notching of the Pulmonary Valve in the Absence of Pulmonary Hypertension

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In a patient with idiopathic dilatation of the pulmonary artery the pulmonary valve echogram showed a prominent mid systolic closing motion or notching indistinguishable from that seen in pulmonary hypertension. Normal right ventricular and pulmonary arterial pressures were recorded simultaneously with echocardiograms of the pulmonary valve.

Echocardiographic recording of valve motion has proved useful in the clinical evaluation of patients with a wide variety of cardiac disorders. Evaluation of pulmonary valve motion is useful in the noninvasive investigation of pulmonary hypertension.[1] In adults with pulmonary hypertension, the pulmonary valve *a* wave is generally diminutive or absent, and the diastolic E-F slope is reduced.[2,3] A mid systolic closing motion or notching of pulmonary valve closure is generally regarded as the most specific echocardiographic feature of pulmonary hypertension,[4] although the reliability of this finding has not been adequately evaluated. Nanda and Gramiak[5] reported the occasional finding of mid systolic notching of the pulmonary valve in apparently normal patients. We describe in this report a patient who had prominent mid systolic notching of pulmonary valve closure in the absence of pulmonary hypertension.

Case History

A 19 year old black youth presented with pneumonia of the left lower pulmonary lobe. He had previously been asymptomatic, and denied any history of heart disease, heart murmur or rheumatic fever. No abnormalities had been detected during a prior physical examination preceding induction into the armed services.

Examination on admission showed a blood pressure of 110/70 mm Hg, a pulse rate of 96/min and a respiratory rate of 24/min. The temperature was 101°F orally. The patient appeared thin and asthenic, and was in mild distress. No cyanosis, clubbing, edema or jugular distension was detected. The left posterobasal lung field showed signs of consolidation. Cardiac examination disclosed a slightly prominent apical impulse 1 cm lateral to the mid clavicular line. Pulmonary valve closure was easily palpated. Auscultation revealed a normal first heart sound. The second heart sound was physiologically split; the pulmonary component appeared prominent. A protodiastolic filling sound was heard in the left lateral decubitus position. A grade 2/6, short, early systolic ejection murmur was heard at the upper left sternal border.

The chest roentgenogram (Fig. 1) showed a left lower pulmonary lobe infiltrate and straightening of the thoracic spine. The cardiac silhouette was prominent, as was the main pulmonary arterial segment. The electrocardiogram was normal except for minimal nonspecific S-T and T wave changes.

M mode echocardiography showed normal chamber dimensions and wall motion. The pulmonary valve E-F slope and *a* wave amplitude were normal, but a prominent closing motion or notch was present during systole (Fig. 2). Cross-sectional echocardiography showed a prominent main pulmonary artery (Fig.

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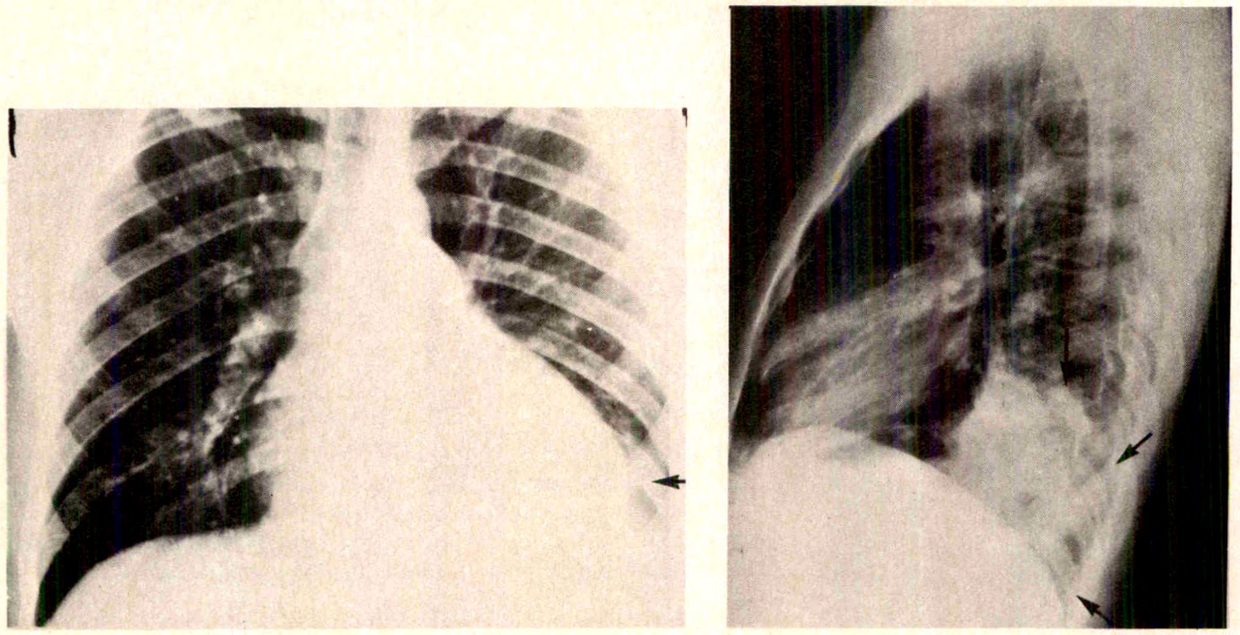


FIGURE 1. Posteroanterior (**left**) and lateral (**right**) chest X-ray films. The cardiac silhouette is prominent, with a cardiothoracic ratio of 56 percent. The main pulmonary arterial segment is enlarged. The normal curvature of the thoracic spine is absent. An infiltrate (**arrows**) is seen in the left lower pulmonary lobe.

3) but was otherwise normal. A technetium pertechnitate radionucleotide blood flow study revealed no evidence of left to right intracardiac shunting.

The patient underwent right heart catheterization after resolution of his pneumonia. All pressures were normal. The right atrial *a* wave was 6, *v* wave 5 and mean pressure 4 mm Hg. The pulmonary capillary wedge pressure was 10 mm Hg. The pulmonary arterial pressure was 19/12 mm Hg (mean 14). Right ventricular pressure was 19/4 mm Hg. Hydrogen inhalation curves revealed no intracardiac shunts. A pulmonary angiogram disclosed dilatation of the main trunk of the pulmonary artery, with normal right and left branches. Catheter-tipped micromanometer pressure recordings were obtained from the right ventricle and pulmonary artery simultaneous with a pulmonary valve echogram (Fig. 4). The valve displayed prominent systolic notching in the presence of normal pressures.

Discussion

Several reports[2–4] have documented that pulmonary hypertension can be detected by observing characteristic alterations in pulmonary valve motion, although

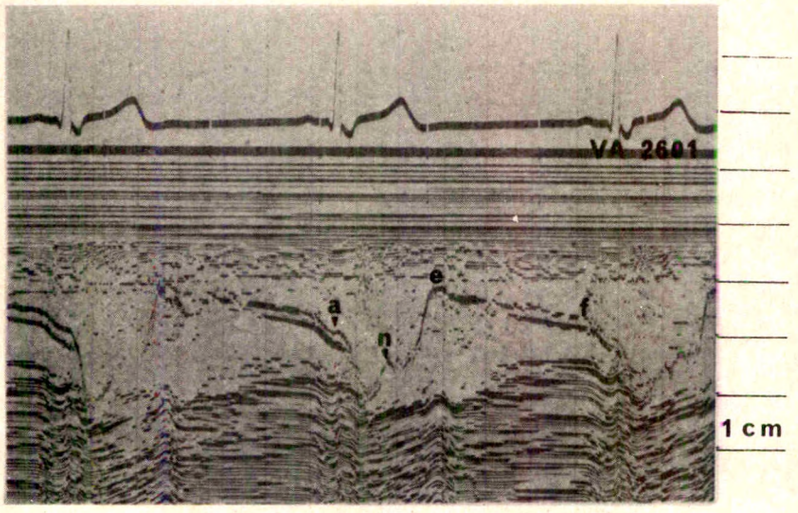


FIGURE 2. Pulmonary valve echogram. The *a* wave (a) is 5 mm in depth and the E-F (e-f) slope is 15 mm/sec. Prominent mid systolic notching (n) is present. Paper speed 50 mm/sec.

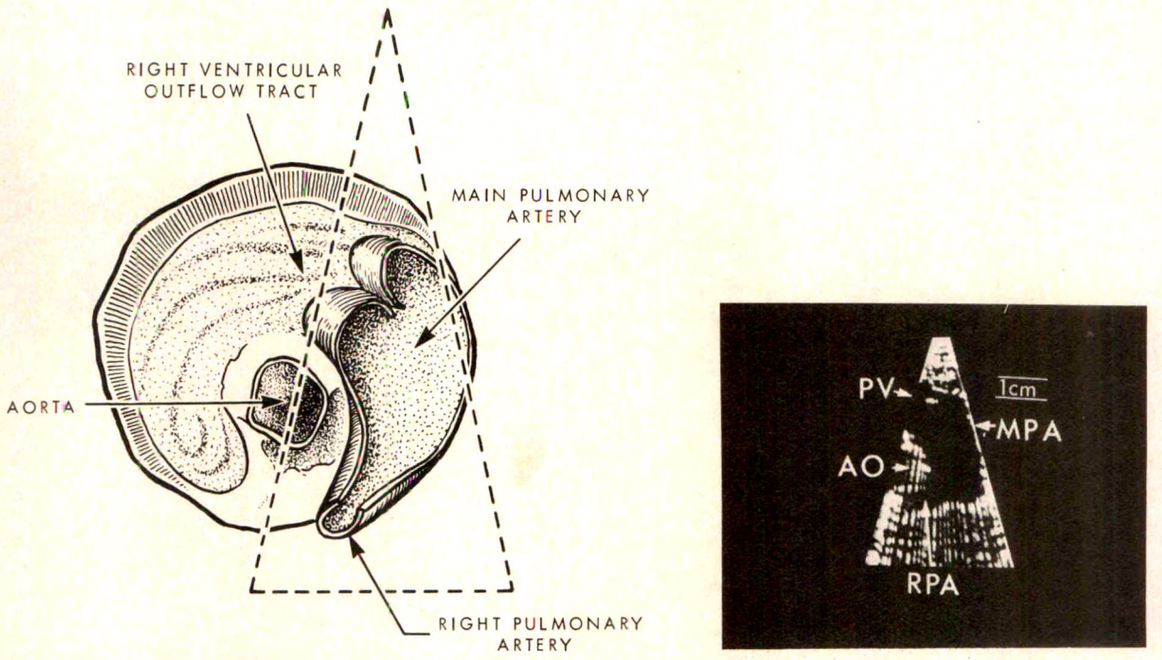


FIGURE 3. Left, a diagram showing the orientation of the cross-section echocardiographic transducer relative to the pulmonary artery and pulmonary valve. The sector indicated by the dashed lines is shown at **right.** The main pulmonary artery is dilated. AO = aorta; MPA = main pulmonary artery; PV = pulmonary valve; RPA = right pulmonary artery.

the reliability and specificity of these findings in large groups of patients is uncertain. Our patient demonstrated a normal pulmonary valve E-F slope and normal *a* wave amplitude but had marked systolic notching of pulmonary valve closure indistinguishable from that seen in pulmonary hypertension. Pulmonary arterial and right ventricular pressures recorded simultaneously with the echocardiogram were normal. Other findings included a "straight back," which probably accounts for the prominence of the pulmonary closure sound on physical examination, and prominence of the cardiac silhouette on chest X-ray film. It seems unlikely that straightening of the thoracic spine would cause mid systolic notching of the pulmonary valve. Dilatation of the main pulmonary artery was shown on pulmonary angiography, cross-sectional echocardiography and chest roentgenography. This finding appeared to be real despite the presence of the "straight back" and seems to be a more likely cause of the patient's mid systolic pulmonary valve notching.

Possible causes of mid systolic notching of pulmonary valve closure: Several physiologic hypotheses could explain the phenomenon of mid systolic notching of pulmonary valve closure. In the presence of pulmonary hypertension, the right ventricle may be unable to maintain a persistent flow of blood against increased pulmonary arterial impedance. Decreasing flow may allow the valve to float toward a closed position during systole. Alternatively, the decreased effective vascular bed seen in pulmonary hypertension could be respon-

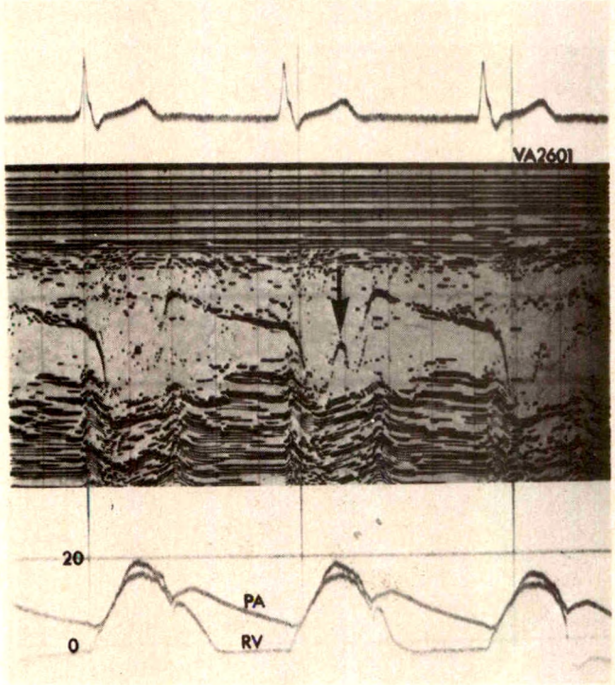


FIGURE 4. Simultaneous pulmonary valve echogram and catheter-tip micromanometer pressure recordings from the pulmonary artery (PA) and right ventricle (RV). Mid systolic notching of the pulmonary valve is indicated by the **arrow.** Simultaneous pressures are normal. Calibration 0 to 20 mm Hg; paper speed 50 mm/sec.

sible for mid systolic notching. Following initial right ventricular ejection into a small vascular tree, the pressure front might be reflected back toward the pulmonary valve as a tidal wave, reaching the valve prematurely and causing a mid systolic closing motion.

A final hypothesis relates perhaps both to the patient presented here and to patients with pulmonary hypertension. Semilunar valve leaflets usually lie immediately adjacent to the walls of the great vessels throughout systole. The diameter of the valve orifice is essentially the same as that of the great vessel. With enlargement of the main pulmonary artery, a feature of pulmonary hypertension as well as "iodiopathic dilatation of the pulmonary artery," blood flowing through the valve orifice may produce eddy currents around the valve, resulting in a closing motion of the valve during systole due to a Venturi effect.

These and other hypotheses must be tested before the physiologic principles underlying mid systolic notching of the pulmonary valve are completely understood. This patient demonstrates that factors other than elevated pulmonary arterial pressure may be involved in producing mid systolic notching of the pulmonary valve. The specificity and reliability of the various echocardiographic features of pulmonary hypertension remain to be established.

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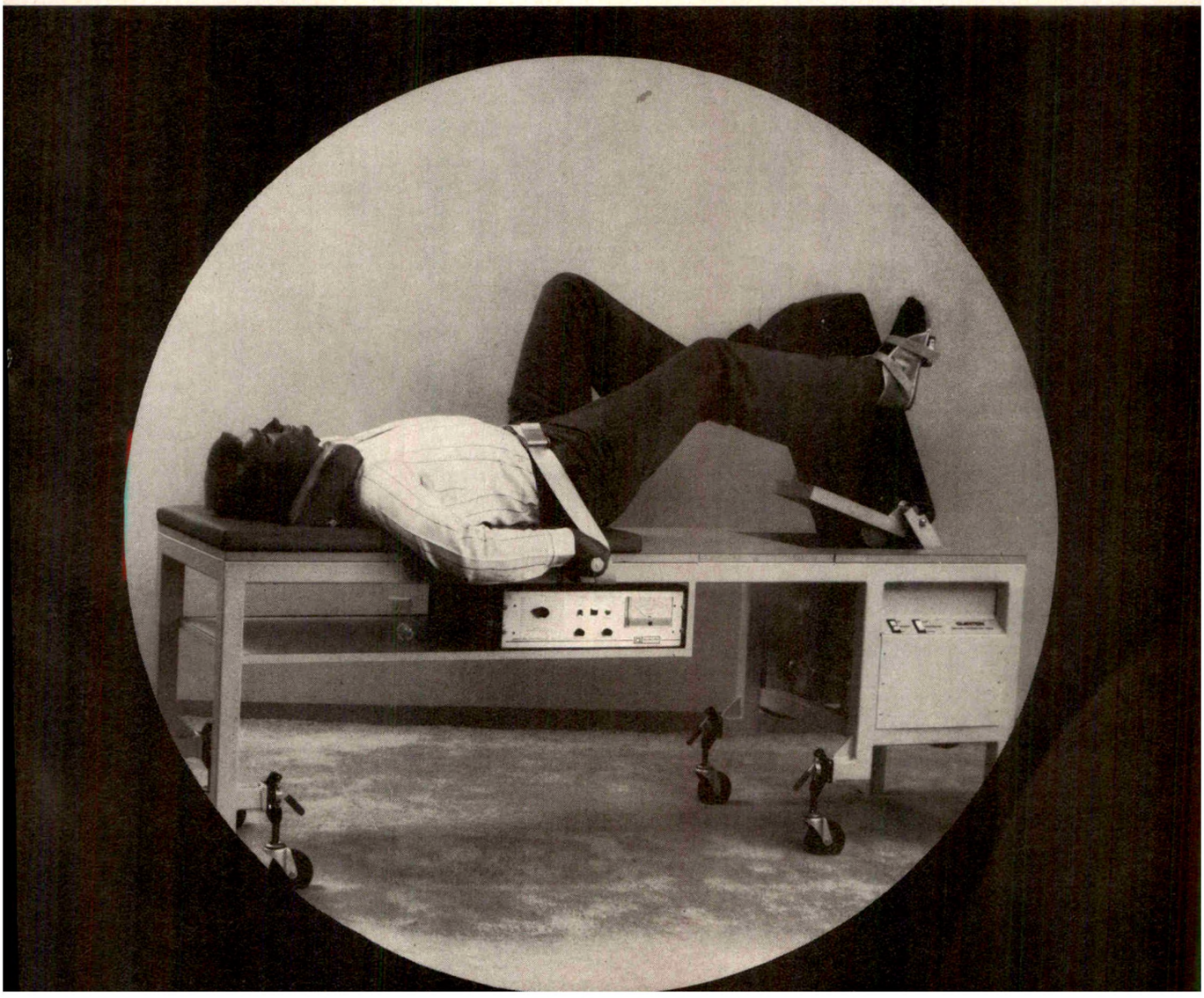
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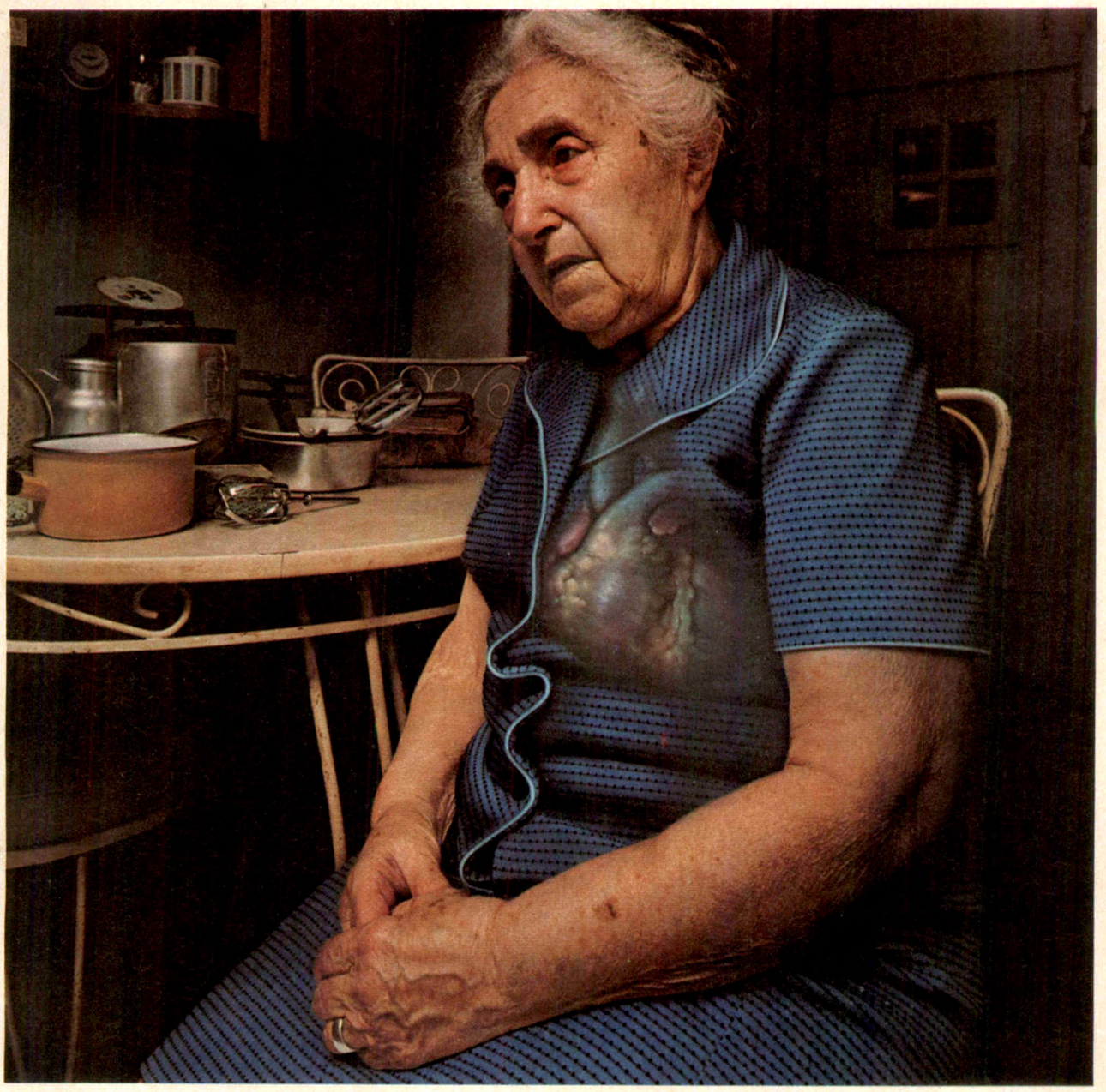
Contraindications: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

Warnings: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

Precautions: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when

BECAUSE IN CARDIAC EDEMA... THERE IS A POINT AT WHICH A GOOD DRUG BECOMES AN INVALUABLE ONE.



the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

Adverse Reactions: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice, (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

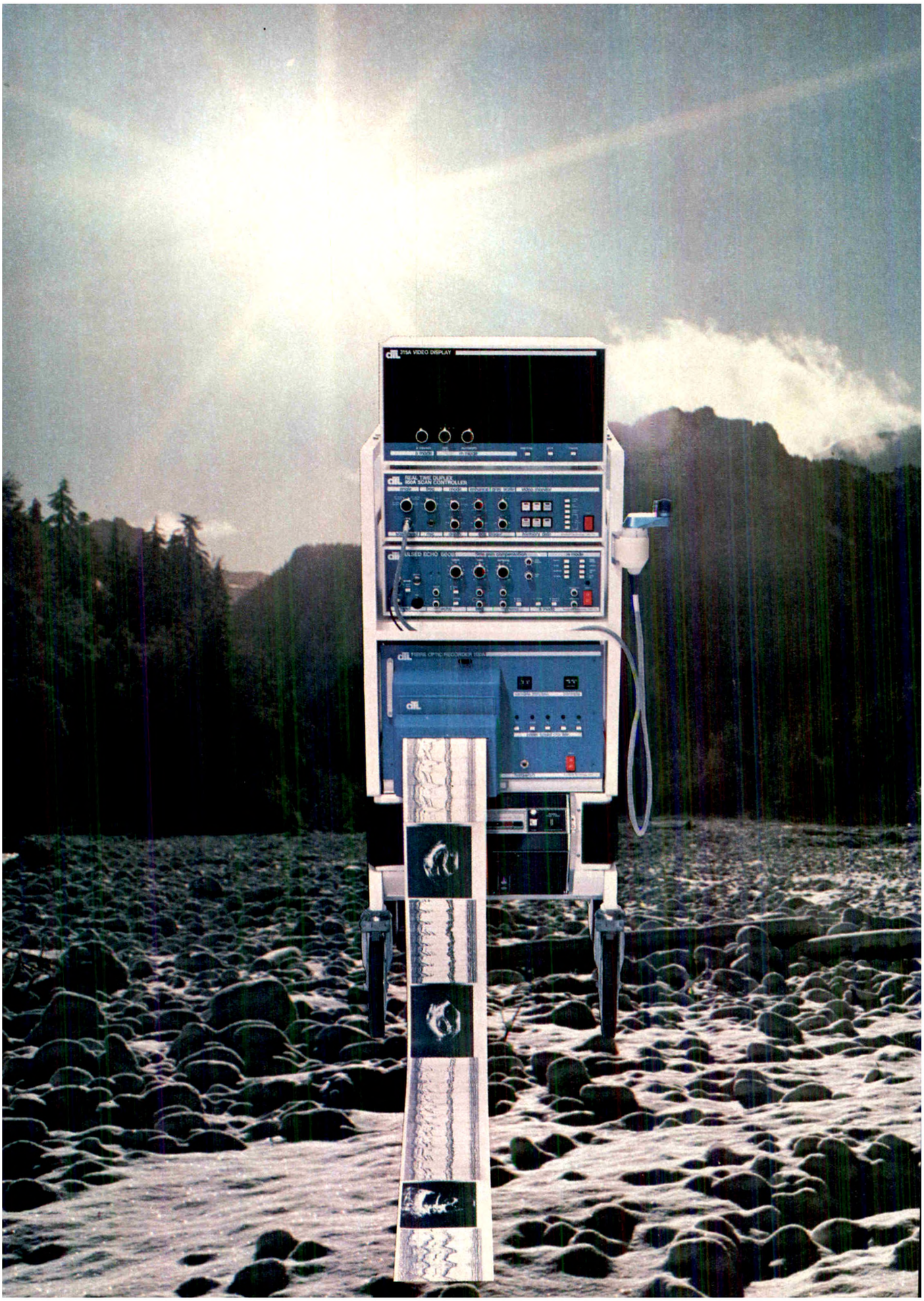
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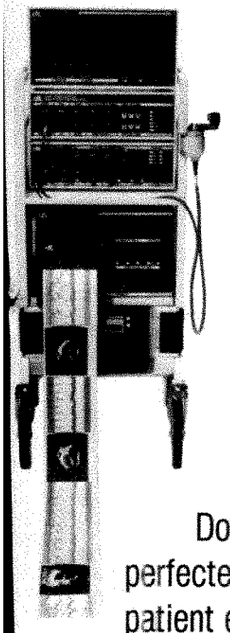
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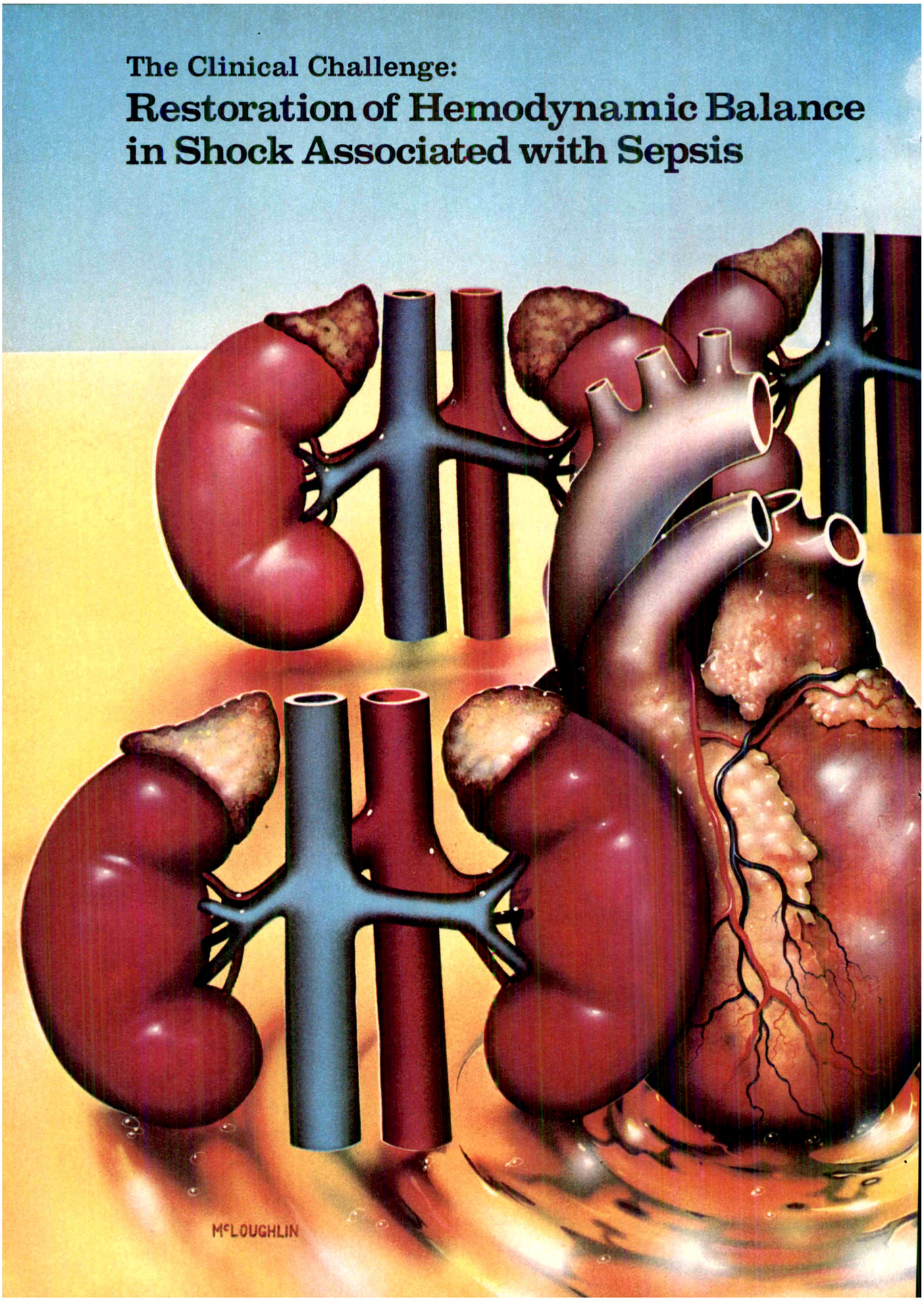
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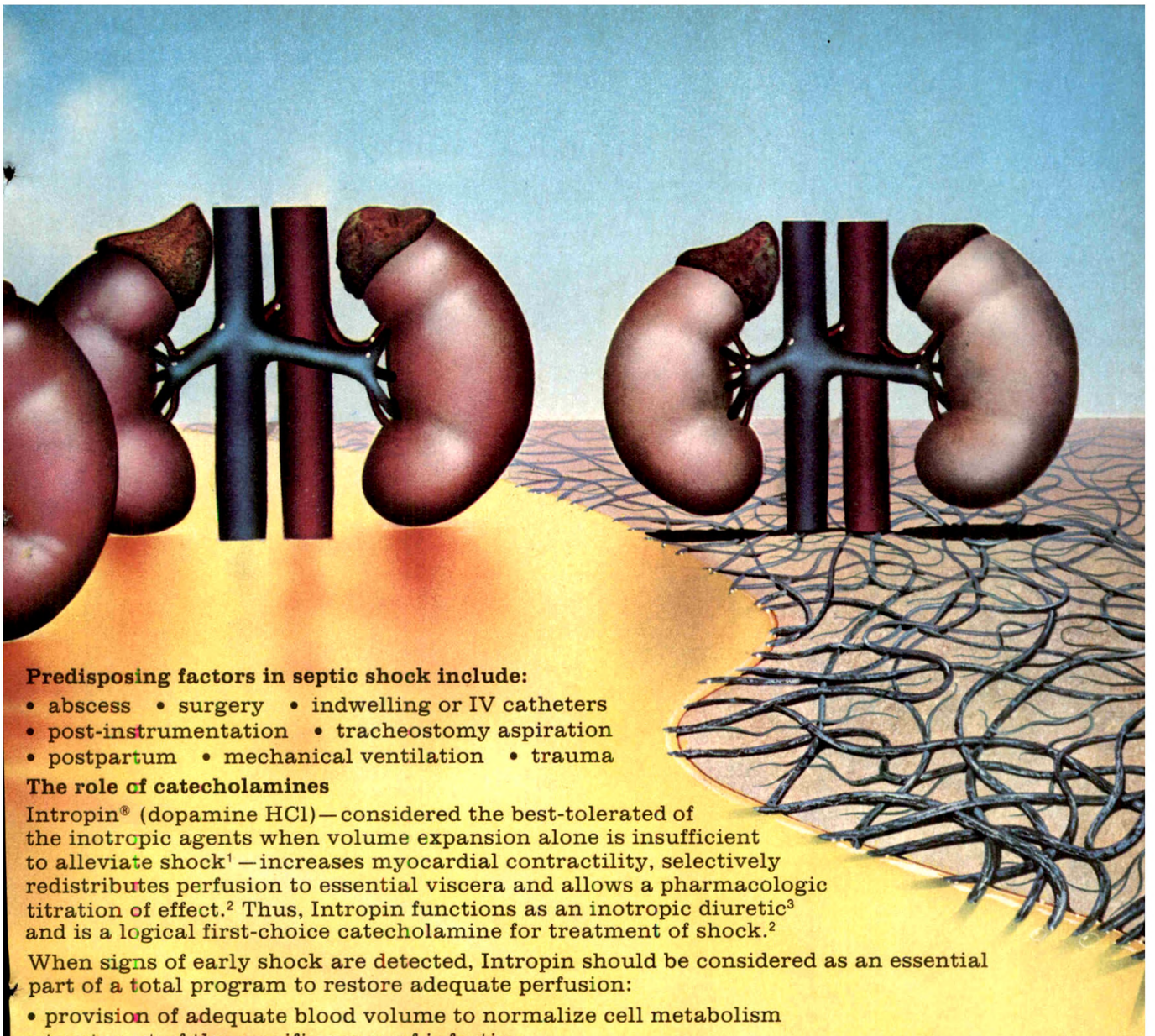
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aTL ultrasound

The Clinical Challenge:

Restoration of Hemodynamic Balance in Shock Associated with Sepsis





Predisposing factors in septic shock include:

- abscess • surgery • indwelling or IV catheters
- post-instrumentation • tracheostomy aspiration
- postpartum • mechanical ventilation • trauma

The role of catecholamines

Intropin® (dopamine HCl)—considered the best-tolerated of the inotropic agents when volume expansion alone is insufficient to alleviate shock[1]—increases myocardial contractility, selectively redistributes perfusion to essential viscera and allows a pharmacologic titration of effect.[2] Thus, Intropin functions as an inotropic diuretic[3] and is a logical first-choice catecholamine for treatment of shock.[2]

When signs of early shock are detected, Intropin should be considered as an essential part of a total program to restore adequate perfusion:

- provision of adequate blood volume to normalize cell metabolism
- treatment of the specific cause of infection
- correction of acid/base imbalance
- redirection of perfusion to vital organs

When volume expansion does not produce adequate patient response, Intropin produces more favorable overall results than either norepinephrine or isoproterenol...and its specific renal and mesenteric artery vasodilating properties make it the most applicable agent in septic shock, if arterial pressure can be maintained.[4]

References: 1. Gunnar, R.M., **Symposium, Use of dopamine in shock,** University of Southern California, Hollywood Presbyterian Medical Center, Los Angeles, May 18, 1976. 2. Reid, P.R. and Thompson, W.L., **Johns Hopkins Med. J.,** 137:276-279, 1975. 3. Rosenblum, R., **Am. Heart J.,** 87:527-530, April 1974. 4. Winslow, E.J., Loeb, H.S., Rahimtoola, M.B., Kamath, S. and Gunnar, R.M., **Am. J. Med.,** 54:421-430, April 1973.

INTROPIN® (dopamine HCl)

A unique response to the clinical challenge of septic shock

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See following page for brief summary of prescribing information.

ARNAR-STONE LABORATORIES, INC.
McGaw Park, Illinois 60085
A Subsidiary of American Hospital Supply Corporation

INTROPIN® (dopamine HCl)
5 ml AMPUL/FOR IV INJECTION

BRIEF SUMMARY OF PRESCRIBING INFORMATION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. It is a white, odorless, crystalline powder, freely soluble in water and soluble in alcohol; sensitive to light, alkalis, iron salts and oxidizing agents. Each ml of sterile, non-pyrogenic INTROPIN Injection contains 40 mg of dopamine hydrochloride (equivalent to 32.3 mg of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

INDICATIONS: For the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Poor Perfusion of Vital Organs—Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. The physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Note that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce a potentiating effect.

Low Cardiac Output—Increased cardiac output is related to the direct inotropic effect of INTROPIN on the myocardium. Increased cardiac output at low or moderate doses has been associated with either static or decreased systemic vascular resistance (SVR) and appears to be related to a favorable prognosis. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in SVR as may occur with isoproterenol.

Hypotension—Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, the drug's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. Administration should be considered as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation. INTROPIN should not be added to any alkaline diluent solution since the drug is inactivated in alkaline solutions. Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage (1/10 the usual starting dose).

Usage in Pregnancy—INTROPIN may be used in pregnant patients when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children—The safety and efficacy of INTROPIN for pediatric use has not been established.

PRECAUTIONS: Avoid Hypovolemia—Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure—If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation—INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site which may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle.

Occlusive Vascular Disease—Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities.

IMPORTANT—Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml of saline solution containing from 5 to 10 mg of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, *phentolamine should be given as soon as possible* after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics—Because of the theoretical arrhythmogenic potential of these agents and the known increase in cardiac autonomic irritability which may sensitize the myocardium, INTROPIN should be used with EXTREME CAUTION in patients inhaling such anesthetics.

Careful Monitoring Required—As in the case of any adrenergic agent, infusion of INTROPIN should be accompanied by close monitoring of urine flow, cardiac output and blood pressure.

ADVERSE REACTIONS: The most frequent include ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Others reported infrequently are aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

WARNING: This is a potent drug—must be diluted before administration to patient.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since the drug's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

CAUTION: Federal law prohibits dispensing without a prescription. Full directions for use should be read before administering or prescribing. September, 1978

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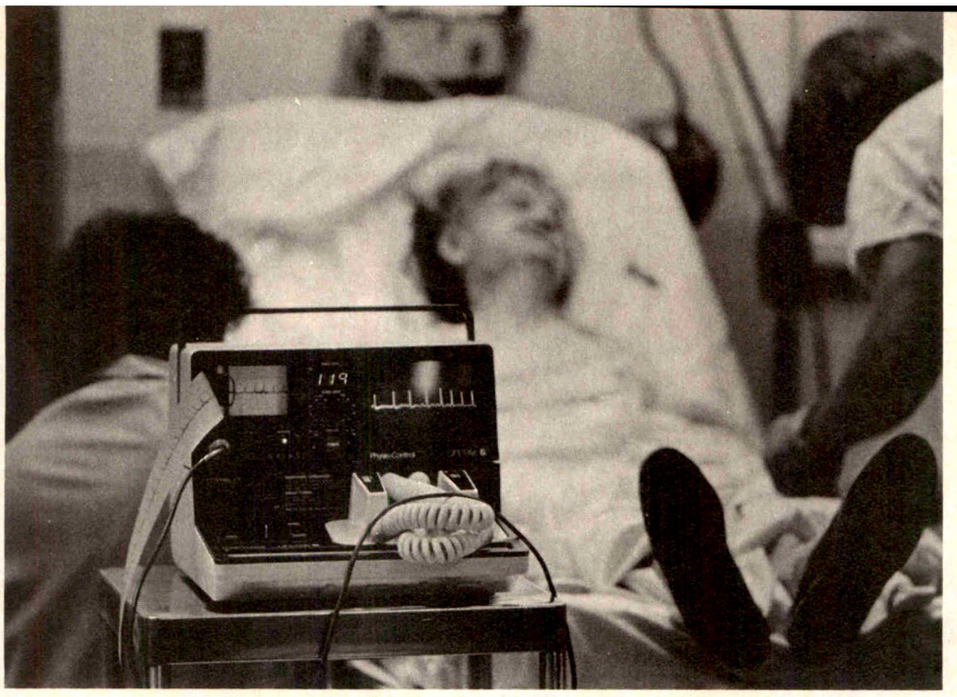
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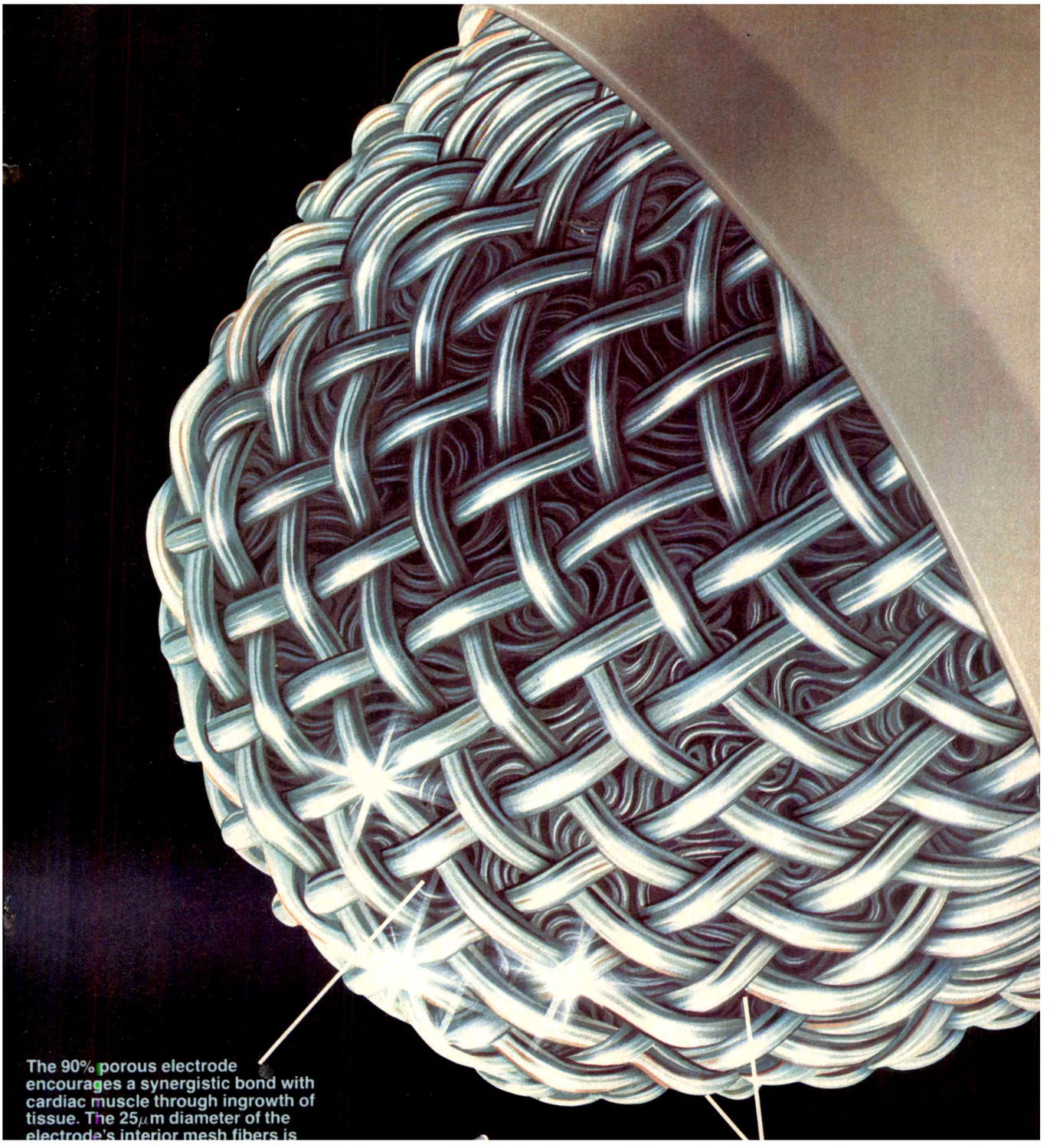
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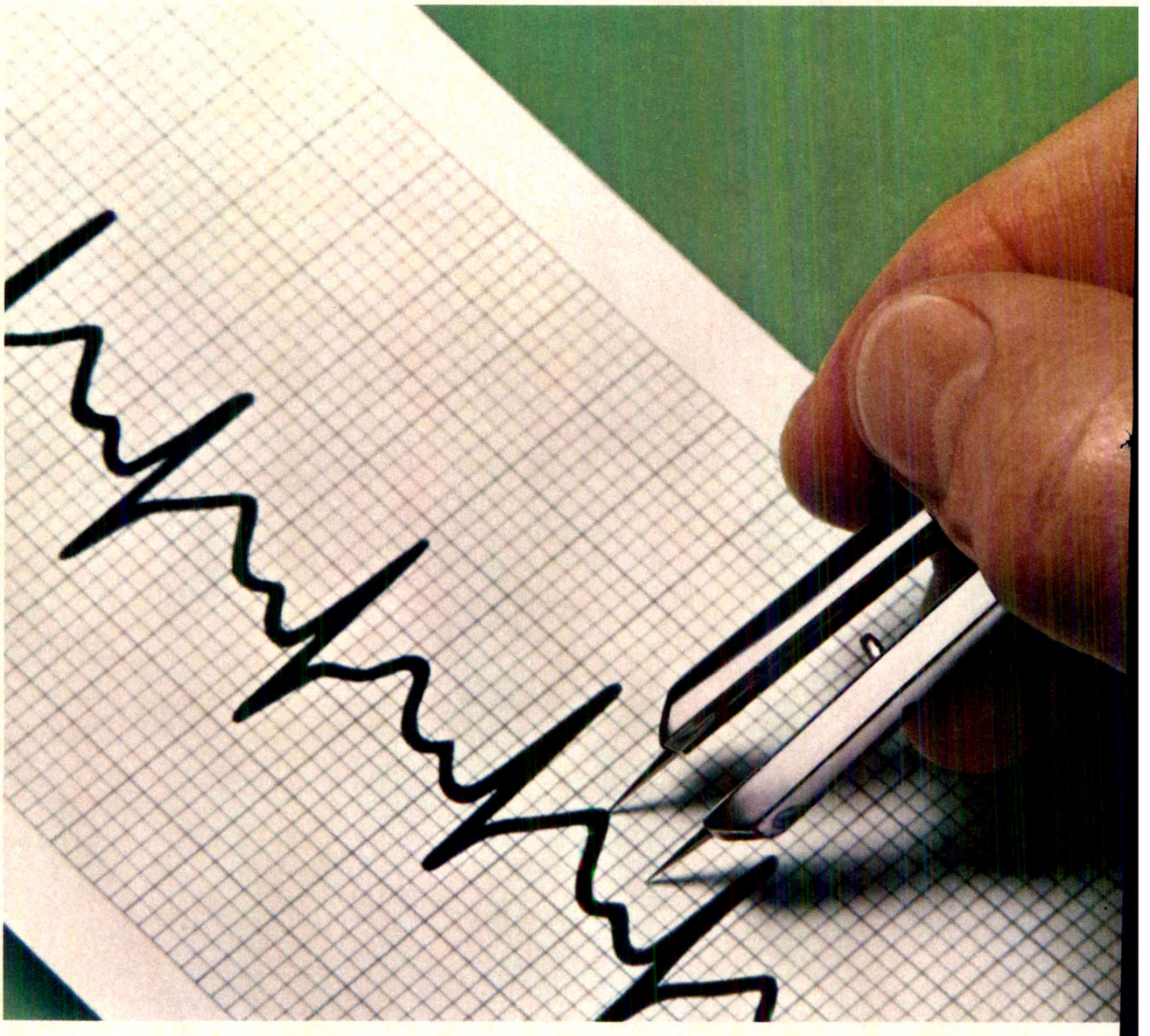
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PERFORMANCE IN CARDIAC ARRHYTHMIAS

EFFECTIVE ALONE OR IN COMBINATION



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INDERAL (propranolol hydrochloride): Successful treatment of supraventricular arrhythmias for over 10 years

INDERAL, used alone or in combination with other antiarrhythmics, has improved or resolved a variety of supraventricular arrhythmias.[1-7]

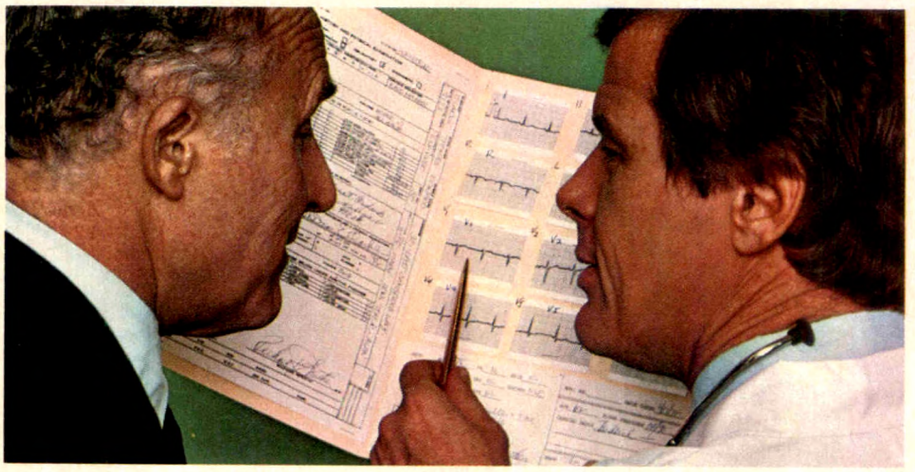
INDERAL alone: Results of use against atrial tachyarrhythmias in one series have recently been reported:

Arrhythmia	Patients	Proportion deriving benefit	
		Complete	Partial
Sinus tachycardia	86	59%	22%
Atrial tachycardia (including paroxysmal type)	154	61%	19%
Atrial flutter	50	54%	32%
Atrial fibrillation	139	53%	26%

Adapted from Coodley and Snyder.[8]

INDERAL is particularly effective in therapy of supraventricular tachyarrhythmias.[9] It slows depolarization of sinus and ectopic pacemaker cells, and retards impulse-conduction in the atria and across the AV node.[1,10,11] In cases where it cannot restore normal sinus rhythm, INDERAL is frequently effective in reducing the ventricular rate.[1-3,12-14] INDERAL may prevent recurrent supraventricular tachyarrhythmias when digitalis and quinidine fail to do so.[9,12] In addition, INDERAL is a useful short-term adjunct for arrhythmias of thyrotoxicosis, when





used with specific therapy. Since INDERAL may mask the clinical signs of hyperthyroidism, abrupt withdrawal should be avoided to prevent exacerbation of the symptoms of hyperthyroidism.

And in combination: INDERAL has also been used to complement the actions of other antiarrhythmic agents.[3-5,8,9,13] The combination of INDERAL and quinidine has suppressed supraventricular arrhythmias that have not responded to either drug alone.[3,9]

When toxic doses of digitalis glycosides occasionally fail to control the ventricular rate in patients with atrial fibrillation or flutter, addition of INDERAL to a digitalis glycoside, with reduction of the digitalis dosage, may prolong AV conduction to the point where satisfactory control of ventricular rhythm is established.[8,15]

INDERAL: Often effective in tachyarrhythmias of digitalis intoxication[2,9,10,14] INDERAL has been found useful in the treatment of certain digitalis-induced arrhythmias that persist following discontinuation of digitalis and correction of electrolyte disturbances, particularly hypokalemia. Its use in this setting may be limited by the presence of significant congestive failure or heart block, and the development of severe bradycardia. (Please see prescribing information on the next page for "Overdosage or Exaggerated Response.")

INDERAL is contraindicated in sinus bradycardia, greater than first degree heart block, and congestive heart failure unless the failure is secondary to tachyarrhythmias treatable with INDERAL. (See prescribing information for complete list of CONTRAINDICATIONS.)

Please see next page for prescribing information.

Ayerst

BRIEF SUMMARY
(For full prescribing information, see package circular.)

INDERAL® Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA) AND THE PHARMACOLOGY OF THIS DRUG

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

INDICATIONS: Cardiac Arrhythmias:

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.

May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias

With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice in clinical situations when cardioversion techniques or other drugs are not indicated or are not effective. INDERAL may be considered if, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL (propranolol hydrochloride) unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma, 2) allergic rhinitis during the pollen season, 3) sinus bradycardia and greater than first degree block, 4) cardiogenic shock, 5) right ventricular failure secondary to pulmonary hypertension, 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL, 7) in patients on adrenergic augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn. If tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA. Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY. The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular*: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short term memory loss; emotional lability, slightly clouded sensorium; and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation; mesenteric arterial thrombosis; ischemic colitis.

Allergic: pharyngitis and agranulocytosis; erythematous rash; fever combined with aching and sore throat; laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis; nonthrombocytopenic purpura; thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL (propranolol hydrochloride) is different for each indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE. At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS. Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE:

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 462—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

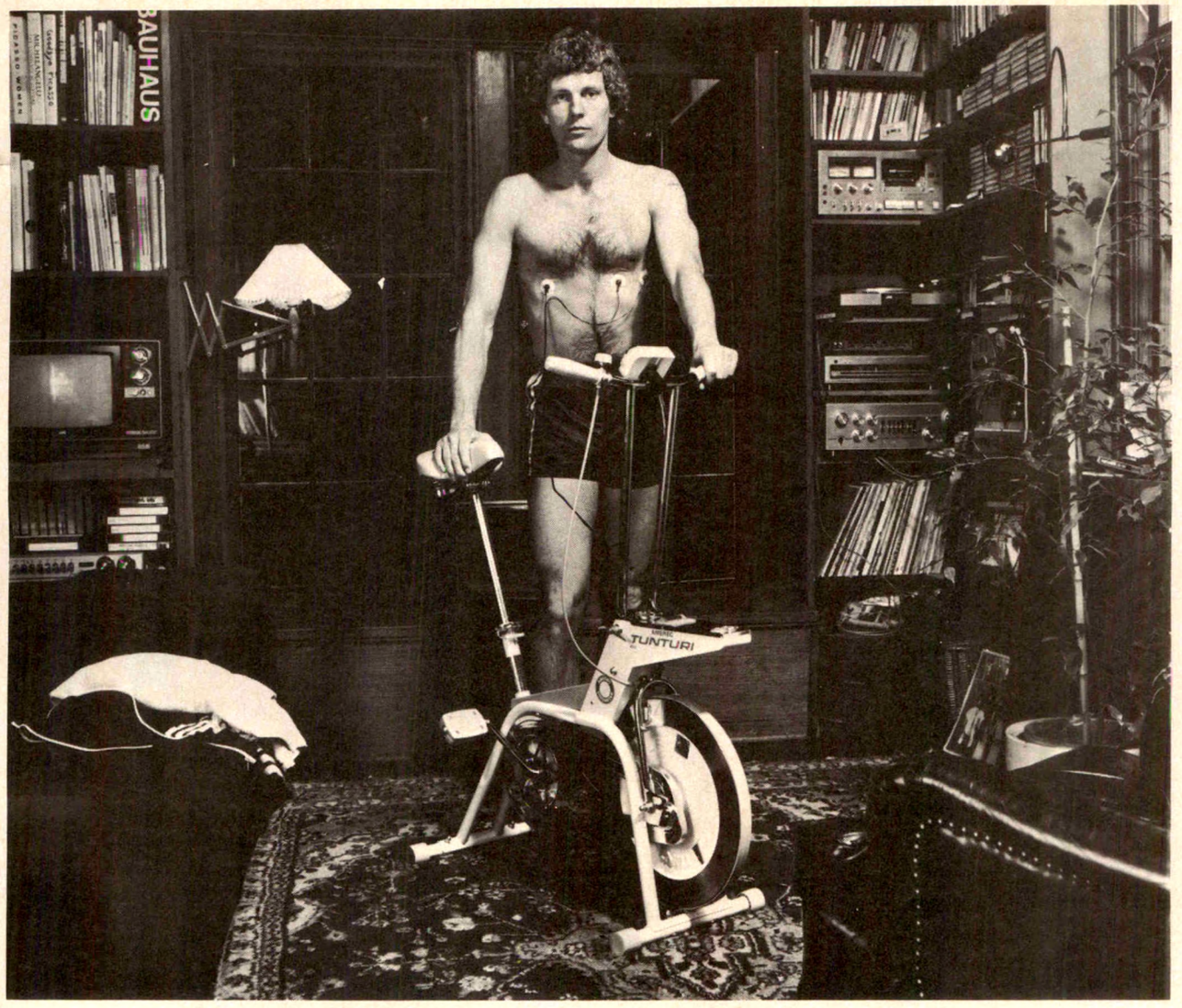
INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10.

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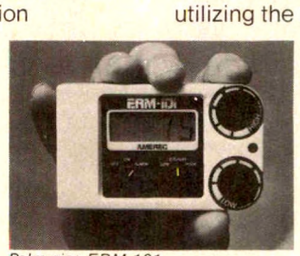


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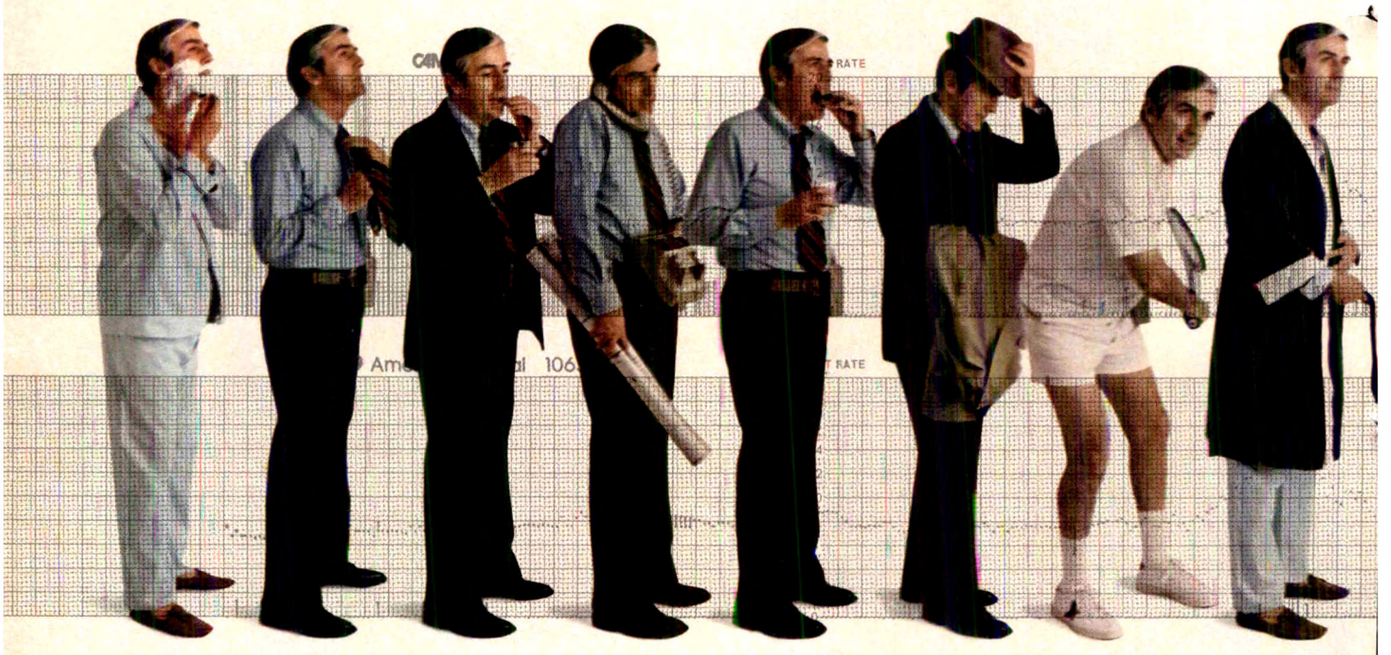
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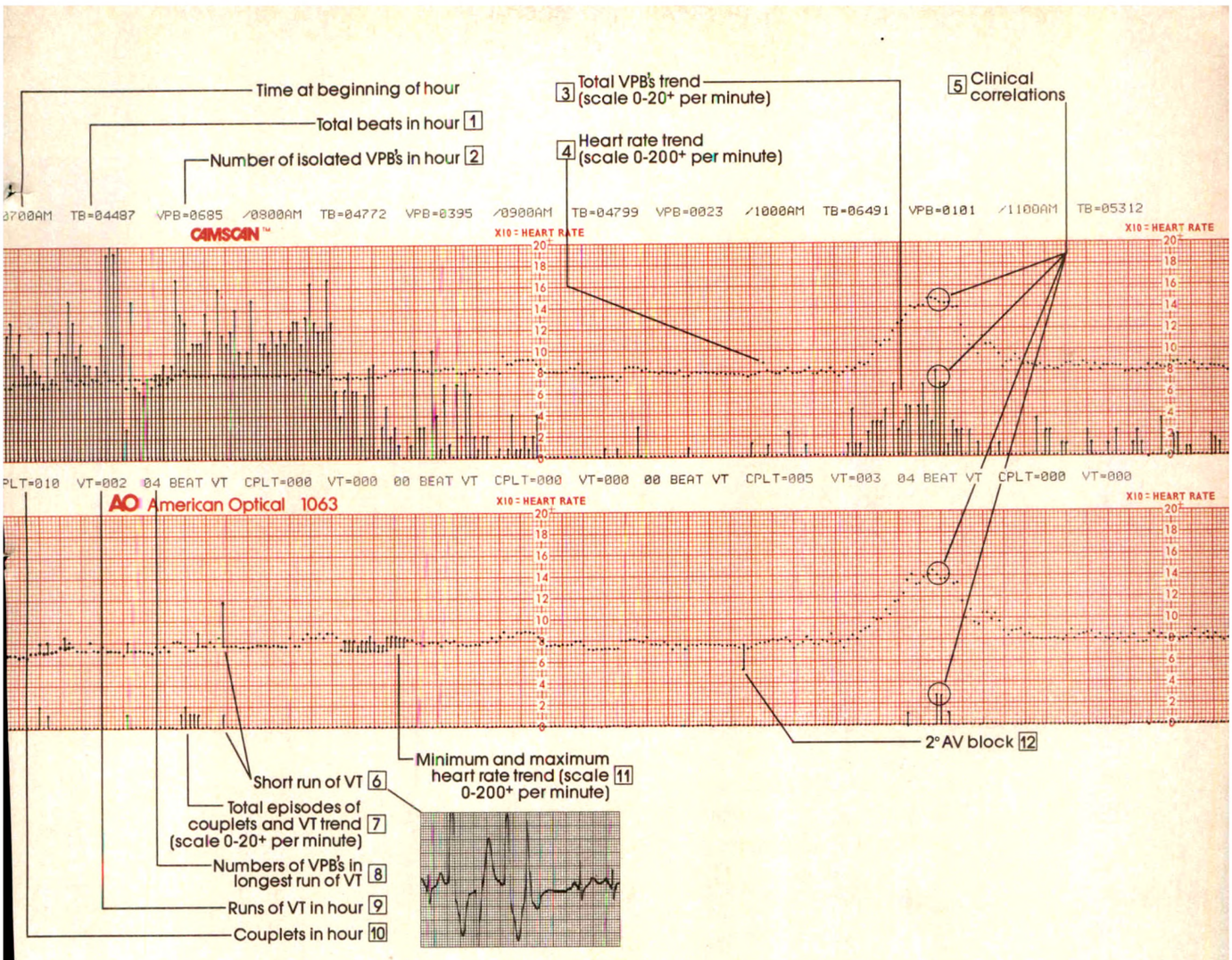
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Disopyramide-Induced Ventricular Fibrillation

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H. ROEBLING KNOCH, MD

York, Pennsylvania

Three cases are described with documented ventricular fibrillation shortly after the patients received disopyramide in moderate dosage. Electrocardiograms showed markedly prolonged Q-T intervals in two patients and a prominent U wave with a prolonged Q-U interval in one patient, but no change in QRS width. Disopyramide-induced ventricular fibrillation appears to be similar to that caused by quinidine and is an indication to discontinue the drug.

Disopyramide is a new antiarrhythmic agent that has enjoyed recent clinical popularity in the treatment of cardiac arrhythmias. It has been shown to be efficacious in suppressing premature extrasystoles and tachycardias of both supraventricular and ventricular origin.[1–4] It has been stated to cause fewer dangerous side effects than quinidine. A case of ventricular tachycardia with a widened QRS complex and a prolonged Q-T interval precipitated by toxic dosage of disopyramide has been reported.[5] We recently encountered three cases of recurrent ventricular fibrillation that closely followed the institution of oral disopyramide therapy in only moderate doses. In each instance the repolarization changes in the electrocardiogram during therapy with this drug were remarkable.

Case Reports

Case I

A 67 year old white woman had a mitral commissurotomy in 1958 for rheumatic mitral valve stenosis. In August 1978 she underwent mitral and aortic valve replacement at this institution for severe aortic and mitral stenosis. On the 1st postoperative day episodic atrial tachycardia and atrial fibrillation developed. Digoxin had been withheld for 72 hours preoperatively. She received 1 mg of digoxin intravenously over a 24 hour period. Therapy with oral disopyramide, 150 mg every 4 hours, was started. Eight hours after the initial dose, recurrent ventricular fibrillation developed (Fig. 1), necessitating repeated defibrillation. The electrocardiogram showed a markedly prolonged Q-T interval (Fig. 2). Serum potassium was 4.2 mEq/liter. Ventricular fibrillation recurred repeatedly during the next 30 hours despite the withdrawal of disopyramide and treatment with lidocaine, propranolol, diphenylhydantoin and procainamide. A temporary pacemaker was then inserted and overdrive pacing successfully instituted. With the patient receiving no medication, subsequent electrocardiograms showed a normal Q-T interval (Fig. 2). She was discharged from the hospital with digoxin, 0.125 mg/day, as her only medication.

Comment: This patient underwent an uneventful double valve replacement complicated by postoperative supraventricular tachyarrhythmia. After the third dose of disopyramide, which was instituted to suppress the atrial arrhythmia, repeated episodes of ventricular fibrillation developed. An electrocardiogram showed a prolonged Q-T interval with a normal QRS duration. The ventricular arrhythmia was finally controlled with overdrive pacing. Electrocardiograms obtained after discontinuance of disopyramide showed a normal Q-T interval and no ventricular irritability.

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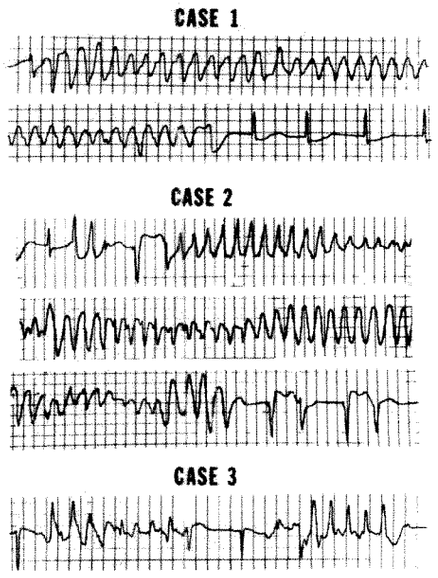


FIGURE 1. Monitor leads showing spontaneous ventricular tachyarrhythmia occurring in three cases during disopyramide therapy.

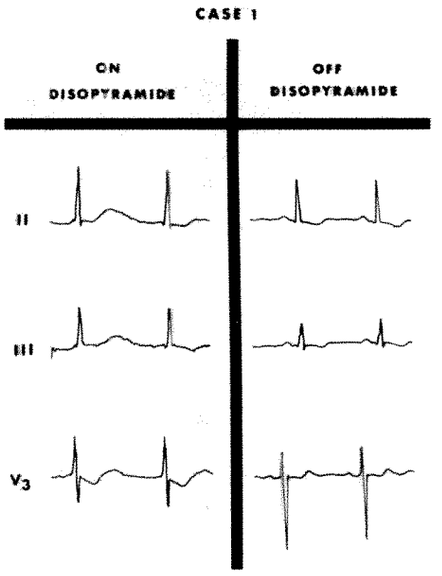


FIGURE 2. Case 1. Electrocardiographic documentation of junctional rhythm with a markedly prolonged Q-T interval while the patient was receiving disopyramide. Normalization of the Q-T interval followed discontinuation of disopyramide.

Case 2

A 61 year old woman had a mitral commissurotomy in 1963 for rheumatic mitral valve stenosis. In 1976, while receiving no digitalis, she had paroxysmal atrial tachycardia with 2:1 atrioventricular (A-V) block. In July 1978, complete heart block with paroxysmal atrial tachycardia again occurred in the absence of digitalis, and a permanent pacemaker was implanted. The patient was given oral disopyramide, 150 mg every 6 hours, and digoxin, 0.25 mg/day. She was readmitted to this hospital in August 1978 because of episodic weakness. The electrocardiogram on admission showed a markedly prolonged Q-T interval (Fig. 3) and episodes of self-terminating ventricular fibrillation (Fig. 1). The serum potassium was 4.7 mEq/liter. Disopyramide was discontinued. There were no further episodes of ventricular fibrillation. A subsequent electrocardiogram during junctional tachycardia showed a normal Q-T interval (Fig. 3).

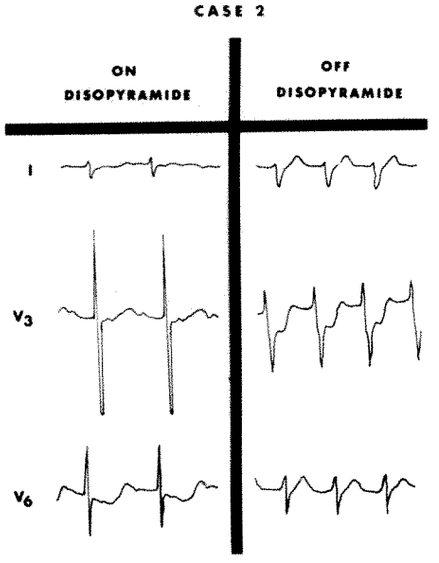


FIGURE 3. Case 2. Selected electrocardiographic leads demonstrating paroxysmal atrial tachycardia with high grade A-V block and a markedly prolonged Q-T interval while the patient was receiving disopyramide. Normalization of the Q-T interval during an episode of junctional tachycardia followed discontinuaton of disopyramide.

Comment: This patient presented with rheumatic mitral valve stenosis and paroxysmal atrial tachycardia with episodes of complete heart block. Treatment with disopyramide produced a markedly prolonged Q-T interval and episodes of self-terminating ventricular fibrillation. Discontinuance of the disopyramide resulted in normalization of the Q-T interval without further episodes of ventricular fibrillation.

Case 3

A 46 year old white woman had prolapsing mitral valve syndrome documented with echocardiography and cardiac catheterization. Holter 24 hour electrocardiographic monitoring in June 1978 showed frequent ventricular extrasystoles with brief bursts of asymptomatic ventricular tachycardia. On August 3, 1978 institution of treatment with oral disopyramide, 150 mg four times daily, resulted in nearly complete suppression of ventricular ectopy. Other medications included a thiazide diuretic drug once daily and a potassium supplement twice daily. On August 9 the patient became pulseless, cyanotic and apneic. Immediate resuscitatory efforts were successful and the patient was transported to this hospital. The electrocardiogram on admission (Fig. 4) demonstrated a prolonged Q-T interval, normal QRS duration and a very prominent U wave and recurrent ventricular tachyarrhythmias (Fig. 1). Serum potassium was 3.7 mEq/liter. Disopyramide was discontinued. Ventricular ectopy and tachyarrhythmia were subsequently suppressed with oral propranolol, 60 mg four times daily, and diphenylhydantoin, 100 mg four times daily. Previous and subsequent electrocardiograms

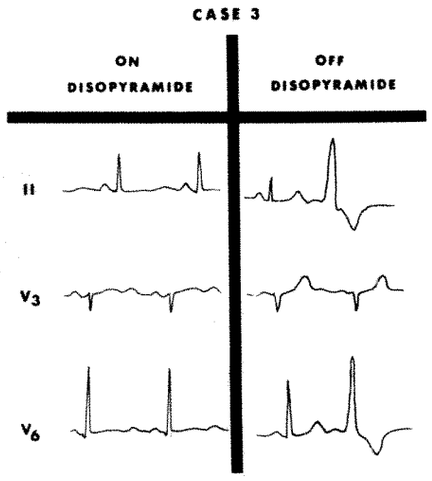


FIGURE 4. Case 3. Electrocardiographic documentation of a prominent U wave with a prolonged Q-U interval occurring while the patient was receiving disopyramide. Normalization of the electrocardiogram followed discontinuance of disopyramide.

showed a normal Q-T interval and much less prominent U waves (Fig. 4).

Comment: This patient presented with a prolapsing mitral valve syndrome with ventricular arrhythmia. Treatment with disopyramide produced a very prominent U wave, prolongation of the Q-T interval and worsening of the ventricular arrhythmia followed by a cardiac arrest. The Q-T interval and U wave normalized after disopyramide was discontinued.

Discussion

Disopyramide is classified as a type I antiarrhythmic agent because it decreases the rate of phase IV depolarization, diminishes myocardial conduction velocity and prolongs effective and functional refractory periods in the atrium, A-V node and ventricles.[6–8] Thus, its electrophysiologic effects are similar to those of quinidine. A well documented instance of a prolonged QRS complex and Q-T interval with ventricular tachycardia, but without syncope, has been reported.[5] This rhythm occurred while the patient was inadvertently receiving a large oral dosage (600 mg every 6 hours) of disopyramide resulting in toxic blood levels. "Quinidine syncope" (ventricular tachyarrhythmia) and marked Q-T prolongation have not previously been reported with usual dosages of disopyramide.

TABLE I

Relation between Administration of Disopyramide, Corrected Q-T interval (sec) or Q-U interval (sec) in Three Cases

State	$Q\text{-}T_c$ Interval (sec) Case 1	$Q\text{-}T_c$ Interval (sec) Case 2	$Q\text{-}U_c$ Interval (sec) Case 3
Receiving disopyramide	0.56	0.54	0.72
No disopyramide	0.38	0.36	0.43

Our patients treated with disopyramide had three types of heart disease: chronic valve disease, postoperative rheumatic valve disease and prolapsing mitral valve syndrome. All three patients had complicated cardiovascular disorders necessitating varied treatment methods. All had been under long-term care, and only Patient 3 had prior documentation of asymptomatic ventricular arrhythmia. Because these three cases of repetitive ventricular tachyarrhythmia were noted in a short time span, the clinical course of the patients was reviewed. It became clear that in these three cases recent disopyramide treatment was associated with the occurrence of ventricular tachyarrhythmia. Marked prolongation of the Q-T interval was present in the third instance. An electrocardiogram obtained after discontinuance of the disopyramide manifested normalization of the Q-T and Q-U intervals (Table I).

Implications: We believe that the recurrent ventricular tachycardia in these three cases represents episodes of quinidine-like syncope precipitated by disopyramide. Patients receiving treatment with disopyramide should be closely monitored for symptoms of ventricular tachyarrhythmia in the manner of patients receiving quinidine.[9,10] Should such episodes occur, the drug should be discontinued immediately. Patients showing disproportionate repolarization changes (prolonged Q-T and Q-U intervals) should be followed up closely and perhaps have the drug withheld.

Acknowledgment

We are grateful to V. L. Tyson for technical assistance.

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Recent Advances in Digitalis Research*

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In view of the exciting recent advances in digitialis research that have afforded physicians an improved understanding of the drug's pharmacology and therapeutic nature, it is particularly relevant that four articles in this issue of the Journal[1–4] focus attention on new knowledge germane to judicious application of the glycosides in the management of cardiac dysfunction in different clinical settings. Following the highly productive investigations of the 1960's elucidating the mechanisms of the beneficial cardiocirculatory effects of digitalis on a physiologic basis,[5] the present era of more fundamental understanding was initiated with Butler's development[6] of digitalis-specific antibodies and glycoside radioimmunoassay, which allowed for the first time an accurate and practical means for the clinical measurement of serum digitalis concentrations.[7] Subsequently, considerable information has been gained[8] about glycoside metabolism, cardiac receptor characteristics, pharmacokinetics,[9] intestinal absorption, dose-contractility response,[10] digitalization,[11] drug interactions,[12] toxicity[13,14] and specific arrhythmic antidotes.[15] In addition, recent biochemical and electrophysiologic studies[16–18] have provided valuable insight concerning the subcell mechanisms of the agent's contractile and toxic actions.

Digitalis in Sick Sinus Syndrome

In this issue of the Journal, Reiffel, Bigger and Cramer[1] report on their investigation of the important clinical consideration of the influence of digitalis on sinus nodal function in patients with sick sinus syndrome. Their findings are in agreement with the previous observations by Vera et al.[19] that digoxin does not exert negative chronotropic effects or cause further prolongation of sinus nodal recovery time. Because sinus nodal recovery testing lacks sensitivity,[20] it is gratifying that our group[19] also found in patients with the sick sinus syndrome that digoxin neither altered heart rate on ambulatory electrocardiographic monitoring nor affected maximal exercise heart rate. The new observation of Reiffel et al.[1] of digoxin-induced slowing of heart rate and prolongation of sinus nodal recovery time in the sick sinus syndrome after administration of atropine indicates an effect similar to the effect of digitalis in the denervated human transplanted heart.[21] Therefore, it appears to us that the post-atropine suppression of sinus nodal function is probably a direct effect of the glycoside rather than an antiadrenergic action,[1] particularly when one also considers that masking rather than augmenting the antiadrenergic activity of digitalis would be expected after vagal blockade. In any event, the finding that digitalis adversely affects sinus nodal function in the absence of parasympathetic function[1] appears to be limited to the special abnormal condition of sick sinus syndrome and to have limited clinical relevance.

It is difficult to appreciate the recommendation[1] that patients with particularly severe sinus node disease be given a trial of intravenous digoxin with electrophysiologic evaluation before long-term use of the glycoside is instituted, because no correlation has been noted[1,19] between sinus nodal function and deleterious effects of the drug; indeeed those patients with marked sinus nodal depression demonstrated improved sinus nodal function after administration of digitalis.[1,19] Nevertheless, we entirely agree with the principal clinically important conclusion that digoxin does not exert adverse effects on sinus nodal function in sick sinus syndrome, and that it can be used safely in patients with this syndrome when it is indicated for treatment of cardiac pump dysfunction or for control of tachyarrhythmias.

Nitroprusside and Digoxin Combined Therapy in Myocardial Infarction With Heart Failure

Raabe[2] in this issue has referred to the previously well documented[22] salutary effects of intravenous nitroprusside on congestive heart failure complicating acute

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myocardial infarction as shown by considerable alleviation of markedly elevated left ventricular filling pressure and elevation to normal values of decreased cardiac output. In his study,[2] the addition of intravenous digoxin resulted in further elevation of the nitroprusside-induced normal cardiac output and further decrease of the nitroprusside-induced normal total systemic vascular resistance without decreasing the moderately increased, but optimal,[23] left ventricular filling pressure. The addition of digitalis in these patients was unnecessary and potentially hazardous because the initially abnormal hemodynamic state had been corrected or optimized with use of nitroprusside alone. If the abnormal hemodynamic state was not satisfactorily improved with use of the vasodilator, the next approach would be to increase the infusion rate of nitroprusside to provide normal cardiac output and optimal left ventricular preload while maintaining normal systemic arterial pressure and ensuring that left ventricular filling pressure does not decline below the upper limit of normal.[24] In the event a cardiotonic agent is required, intravenous dopamine or dobutamine should be utilized.[25]

That the moderately elevated left ventricular filling pressure was not diminished by digitalis while the cardiac output increased is highly unusual. Thus the increased left ventricular end-diastolic pressure should have decreased after digoxin for at least two reasons: (1) The greater stroke output afforded by the reduced impedance to left ventricular ejection and enhanced contractility decrease the chamber's end-diastolic pressure,[22] and (2) the sympathetic withdrawal that accompanies an increase in cardiac output in patients with heart failure results in systemic venodilation[26] as well as the decrease in systemic vascular resistance that occured in the patients in this study. Parenthetically, we point out that when decreased cardiac output is not increased by digitalis, as may occur in a severely infarcted left ventricle unable to respond to the cardiotonic agent, the cardiac output may decrease further[27] because the moderate direct systemic arteriolar constrictor action of digitalis is not overbalanced by greater indirect vasodilation due to sympathetic withdrawal,[28] rather than because the drug's direct effect of systemic arteriolar constriction precedes its direct effect of positive contractility[27]; the direct vasoconstrictor action occurs simultaneously with the direct positive inotropic action of the glycoside.[29]

Digitalis is no longer considered an agent of first choice in the treatment of congestive heart failure due to myocardial infarction.[23] A diuretic drug or a long-acting nitrate is used initially when left ventricular filling pressure is excessively elevated and cardiac output is normal[23]; nitroprusside (with dopamine or dobutamine if necessary) is used initially when left ventricular end-diastolic pressure is excessively increased and cardiac output is substantially decreased.[23] Furthermore, the beneficial effects of digitalis are inconsistent in heart failure due to myocardial infarction[30]; the ischemic myocardium is unresponsive to the drug at levels of hypoxia at which dopamine still fully exerts its direct positive inotropic action,[31] and there is probably increased arrhythmogenesis caused by digitalis in the freshly necrotic myocardium.[14]

Digitalis Effects on Myocardial Ischemia in Chronic Coronary Disease

The crucial effect of digitalis on myocardial oxygen consumption in chronic coronary artery disease is examined in patients with stable angina pectoris by Loeb, Streitmatter, Braunstein, Jacobs, Croke and Gunnar[3] in another article in this issue. Left ventricular oxygen demand is predominantly governed by interplay among three hemodynamic-related determinants: (1) intramyocardial tension (afterload [product of systolic blood pressure and chamber radius]), (2) contractile state, and (3) heart rate.[8] However, Loeb et al. found that global energetics were unaltered by ouabain in hearts with a normal or a depressed ejection fraction. These findings are unexpected; one would anticipate that the glycoside would increase cardiac energetics in the normal functioning hearts and decrease cardiac energy demand in the abnormally performing hearts.[32]

In the normal heart the principal action of digitalis on the three determinants of cardiac oxygen requirements is to increase contractility; because the positive inotropic effect of the glycosides elevates myocardial oxygen needs in the normal heart (as is the case in one of the two groups studied by Loeb et al.[3]), digitalis should have elevated myocardial energetics.[8] In contrast, digitalis reduces overall myocardial oxygen consumption and increases cardiac efficiency in the dysfunctioning heart. Thus, in the enlarged heart with abnormal function, left ventricular wall tension is diminished by the decrease in heart size that accompanies the positive inotropic action of the glycoside. In terms of cardiac oxygen needs, this indirect reduction in wall tension together with the indirect decline in the relatively high heart rate due to sympathetic withdrawal is substantially greater than the direct increase in contractility produced by digitalis.[8] Therefore, in chronic ischemic heart disease with ventricular dysfunction (as in the other group studied by Loeb et al.[3]), digitalis should have exerted an antianginal effect. This improvement by digitalis in myocardial energetics in the dysfunctioning heart is not a fundamental property of the agent[8]; rather, in this condition, it overrides the increased need for oxygen normally associated with the direct positive inotropic action of the glycoside.

The inability of Loeb et al.[3] to demonstrate these anticipated results of the disparate effects of digitalis on cardiac aerobic metabolism in the two patient groups was probably due to insensitive methodology. Further, that concordant hemodynamic alterations produced by digitalis were not obtained adds to the difficulty in assessing these data concerning myocardial energetics. In addition, their study is lacking in the most critical aspect of myocardial energetics requiring examination in patients with coronary artery disease; their evaluation of only global ischemia fails to permit analysis of the metabolic and mechanical effects of digitalis on the

segmental regions of left ventricular ischemia characteristic of this disease.

Digitalis Effects on Abnormal Segmental Mechanics in Coronary Artery Disease

The final paper on digitalis in this issue, by Kleiman, Alderman, Goldman, Ingels, Daughters and Stinson,[4] explores the effects of intravenous digoxin on regional dyssynergy and left ventricular function in patients with chronic coronary heart disease. Segmental movement and global function were derived by dynamic fluoroscopic analysis of seven mid-wall metallic markers placed at intervals in an attempt to outline the left ventricular silhouette and to establish transverse chamber axes. As judged by this difficult technique, the investigators were unable to demonstrate major beneficial effects of digitalis on regional wall shortening in these patients with minimally abnormal left ventricular performance.

In contrast, patients with stable coronary heart disease evaluated at our institution[33] with complete left heart catheterization and ventriculography performed before and approximately 1 hour after intravenous administration of ouabain demonstrated considerable enhancement of left ventricular function and improvement in segmental dyssynergy. In additional studies[34] on the effects of digitalis on segmental contraction abnormalities, we determined the extent of contractile response in infarcted, ischemic and normal areas in the intact canine heart. Intravenous ouabain, given 15 minutes after a stable state had been achieved after coronary occlusion, produced positive responses in all areas, expressed as percent increases in tension in each of these zones as measured with strain gauge arches (infarcted area 13 percent, ischemic area 25 percent, normal area 27 percent). Thus, the acutely ischemic myocardium responds to digitalis, and the positive inotropic action of the agent decreases with increasing degrees of ischemia. Also relevant in this regard are studies in experimental animals[35] showing that raising myocardial oxygen requirements in the normal heart by stimulating contractility with digitalis increases the extent of left ventricular ischemia and necrosis that follows subsequent coronary occlusion. In contrast, in the presence of ventricular dysfunction and cardiomegaly, treatment with the glycoside before coronary arterial obstruction reduces the size of myocardial ischemia and infarction.

Conclusions

The fundamental therapeutic action of digitalis is stimulation of ventricular contractile state. The expression of this increased contractility is dependent on the integrity of cardiocirculatory status when the glycoside is administered. Thus, by interplay between direct and indirect cardiac and vascular effects, variable and even opposite changes in cardiac output, peripheral circulatory dynamics and myocardial oxygen consumption can occur. At the subcell level, the positive inotropic property of digitalis appears to result from glycoside-induced enhanced intracell influx of calcium produced by the drug's action on the cardiac cell membrane. In contrast, transmembrane fluxes of sodium and potassium underlie the electrical properties of the glycosides. Future research should clarify the nature of the digitalis receptor and further define the subcell contractile and toxic mechanisms of the agent, as well as elucidate more completely the modified actions of the glycosides in specific types of cardiac diseases as exemplified by the four studies reported in this issue of the Journal. Lastly, it is of considerable importance to formulate the most judicious medical management for heart failure refractory to conventional therapy with digitalis and diuretic drugs,[36] particularly in view of the current interest in systemic vasodilators and innovative new cardiotonics.

Acknowledgment

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LETTERS TO THE EDITOR

INTERSPERSED ADVERTISING

Advertising is an American way of life, and all the major medical journals in the United States subsist in part on advertising from various companies promoting drugs or hard or soft ware. As a subscriber to *The American Journal of Cardiology*, I have noted a disturbing trend toward the conversion of the format of the Journal to that of a "throw-away" type, with a heavy sprinkling of advertising within the main body. For example, in four consecutive September issues of the Journal I noted the following frequency of inter-article advertising: 1975 one advertising break, 1976 one break, 1977 three breaks and 1978 three breaks. The first inter-article advertising break in the September issue of 1978 contains advertisements from no fewer than 13 different companies, all trying to capture the weary eyes of the reader.

Because complete abolition of advertising in American medical journals is an impossibility, I propose that a respected journal such as yours adopt the format of *Circulation, Annals of Internal Medicine* and *The New England Journal of Medicine*, among others, of disallowing inter-article advertising inserts, and permitting advertising only before and after the main body of the text.

Djon Indra, MD
Hilo, Hawaii

REPLY

Dr. Indra raises valid points about the interspersion of advertising between complete papers of the Journal. As Publisher, I would like to share a few thoughts regarding the rationale for this policy.

The field of medical publishing has been marked by a plethora of developments that have added new dimensions to established methodologies. In the past few years alone more than 70 new medical magazines have been introduced. Research indicates that in some cases they are receiving a degree of attention from physicians. As a result, pharmaceutical and medical equipment firms are faced with the question whether to settle for good advertising visibility in a questionable reading environment or questionable advertising page visibility in an outstanding environment such as that of *The American Journal of Cardiology*.

When we made the decision to allow limited interspersion of advertising between sections of the Journal we considered our responsibilities in this order of priority. First, our reader, the physician who now pays $32 a year to receive our Journal, and second, the advertisers, who make it possible for us to publish the Journal at that subscription rate. Without advertising, subscription costs would at least double.

We asked ourselves, and through reader research, what the net effect would be of changing our "stacked" advertising placement policy. We discovered that, if the change were handled in the proper fashion, editorial readership would be affected neither negatively nor positively. Reaction from subscribers has borne this out. Our renewal rate on subscriptions continues to be very high (over 85 percent), and the Journal's circulation is increasing at a dramatic rate. As a result of increased advertising support we have been able to publish more papers more quickly than ever in our history. Frankly, unless we provide advertising exposure potential to reputable firms we really have little right to seek their advertising support. This policy in *The American Journal of Medicine, The American Journal of Surgery* and *The American Journal of Cardiology* has benefited our readers and the industry without compromising either.

Louis F. Le Jacq
Publisher
Yorke Medical Group

MORE ON CORONARY BYPASS SURGERY—I

I have just read the three editorials by Loop,[1] Hultgren[2] and Braunwald[3] and their co-workers on the subject of coronary bypass surgery. I am aware that the subject has had a wide airing, but perhaps I may be permitted a few comments since I was one of the Veterans Administration Chiefs of Cardiology who, in 1970, declined to participate in the VA study, though we were already active in this form of surgery. The decision was not taken lightly, and there were several reasons for it. Important among them was the evident variability in the quality of the surgery I observed within the one institution, a consequence of the requirements of the university teaching program. I would, for instance, see on one day a general surgical resident who was rotating through the VA cardiovascular surgical service putting in the sutures of the coronary anastomoses. Granted, he was doing it under supervision, but as far as I was concerned, it was still a neophyte pair of hands. On another day, it would be the Chief of Service. I failed to see how any meaningful conclusions, with wide applicability, could emerge from my sending out data from these cases into a common pool, and I foresaw the whole study as likely to be an expensive and time-consuming effort without valid conclusions.

It is of no importance whether the personal decision was right or wrong. It is of considerable importance whether the general reasoning is right or wrong. The stark question "Does coronary bypass surgery prolong life?" is one that in itself is meaningless unless the conditions are defined. There is no such thing as "an operation" except as an abstraction from reality: What is real is a particular procedure performed by a particular person of particular skills in particular circumstances. The fallacy of the approach exemplified by the VA study is that so few of the variables can in fact be controlled. There is much more involved than the age of the patient, the ejection fraction and the number of coronary vessels seen to be diseased in the angiogram. The question "Does coronary bypass surgery prolong life?" nevertheless continues to be asked as if it had a general answer, and I submit that there is none.

The question asked must therefore be defined very carefully, and could be any one of the following: (1) Does coronary bypass surgery prolong life when performed by a highly skilled surgeon in ideal circumstances? (2) Does coronary bypass surgery prolong life when performed by a given surgeon at a given VA hospital? (3) Does coronary bypass surgery prolong life when performed by Dr. X in Hospital Y?

It is of no particular relevance to know that the operative mortality in the VA study "compares favorably with the surgical experience of many large surgical centers in the U.S. during 1972 to 1974," [2] at least as far as answering any of these specific questions in concerned, although such comparisons serve to distract attention from the real issues.

The VA study is another worthy attempt to make a silk purse out of a sow's ear, and (may I be forgiven the double metaphor) has turned out to be a pig in a poke. The data, appropriately arranged, can be applied only to an attempt to answer question 2 above.

The more critical issue remains the one that is revealed by another failure of a carefully designed randomized controlled prospective study to answer, to general satisfaction, the question that it set out to answer. It is generally assumed that this approach is the one that is most likely to lead to the establishment of "the truth," on the predication that "the truth" exists and that there is an answer to every question. Loop et al.,[1] for instance, throw a sop to Cerberus by stating "No clinician argues with the potential validity of this investigative method. Clinical trials have enormous value." Chalmers has argued passionately in favor of the methodology, as a consequence of which he has been called "the high priest among the randomizer theologians"—expressing incidentally the cult nature of the affair. Feinstein[4] has said, in relation to the collection of vital statistics, that "the most lamentable aspect of the fundamental problem, however, is the credulity and complacency with which egregiously defective statistics are accepted, used and disseminated as the basis of conclusions about so many major diseases. . . ."

Despite the assertion of Loop et al., there are a few clinicians who argue with the validity of the method and consider that the repeated failure of such studies to convince lies not in bad design or bad performance but in the basic invalidity of a method that involves the pooling of disparate data and the concept of "controls." Sir Peter Medawar, himself a distinguished scientist, has stated his opinion. In discussing the nature of medical activity in terms of the broad demarcation between the "natural sciences" and "what can only be described as the 'unnatural sciences," he writes as follows[5]: "It will at once be recognized as a distinguishing mark of the latter that its practitioners try most painstakingly to imitate what they believe—quite wrongly alas for them—to be the distinctive manners and observances of the natural sciences. Among these are (a) the belief that measurement and numeration are intrinsically praiseworthy (the worship, indeed, of what Ernst Gombrich calls 'idola quantitatis'); (b) the whole discredited farrago of inductivism—especially the belief that facts are prior to ideas and that a sufficiently voluminous compilation of facts can be processed by a calculus of discovery in such a way as to yield general principles and natural-seeming laws; (c) faith in the efficacy of statistical formulae, particularly when processed by a computer—the use of which is interpreted as a mark of scientific manhood."

The retitling by Loop et al. of Braunwald's editorial "Coronary Artery Surgery at the Crossroads" to "Randomized Prospective Studies of Coronary Artery Disease at the Crossroads" might with profit be further modified to "Randomized Prospective Studies at the Crossroads." It is about this that debate is needed, rather than about the attempt to answer questions that, as posed, are unanswerable. If the VA study leads to such a dialog, it will have at least performed that signal service.

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MORE ON CORONARY BYPASS SURGERY—II

The recent trio of editorials testifies to the continuing argument over the exact place of coronary bypass surgery. The Cleveland Clinic group make what might be telling criticisms if they had not been ably answered by Hultgren and colleagues. In this context, observer variability and indeed the argument over the Veterans Administration's coronary angiograms are somewhat mitigated by the fact that randomization should have distributed their quality levels equally in both the surgically and medically treated patients.

Braunwald's editorial has also ably countered the comments of Loop and colleagues. The point here is, however, that this dispute (not to mention the volume of literature on this subject in the past few years) need not have taken place. Braunwald mentions the need for "randomized clinical trials." This is the crux of the problem, but only a part of the general picture.

The campaign for randomized trials of both coronary surgery[1a,b] and other cardiac surgery (aortic stenosis,[1c] Vineberg implants[1d]) began with a series of letters in 1970[1] when it became obvious that bypass was to become a growth industry. The first formal essay analyzing the problems and indicating the urgent need for controlled trials appeared in *The American Heart Journal* in February 1971[2] and was followed by Braunwald's editorial in *Hospital Practice*.[3] Despite these efforts and subsequent attempts to point out for surgery what is an accepted fact in medicine, the number of surgical procedures has progressively burgeoned with a torrent of published reports. Why does this continue? It is clear that most surgeons and their more enthusiastic medical colleagues deeply believe in the efficacy of coronary bypass (ultimately justified, at least for symptomatic relief and for left main coronary occlusion). One cannot deal directly with such feelings in persons who are honestly convinced that what they are doing is best for their patients. The problem was, is (and will be unless changed) the malfeasance (no other word will do) of the natural referees of medicine—journal editors and reviewers and the evaluators of abstracts for national meetings. Had they applied standards comparable with those demanded of controlled trials of medical therapies *from the outset*, it is likely that we would have had better answers and much less argument by this time.

I have only one cavil with Braunwald's excellent analysis of the situation. He proposes that prospective randomized trials be performed "after pilot studies." I hope he means pilot studies in animals. Chalmers[4] has analyzed the "pernicious effect of pilot studies," and all interested parties are encouraged to check this reference. He demonstrated that it is possible to randomize patients for any kind of therapy from the very outset. Random allocation in pilot studies would tend to make them conclusive, while permitting 50 percent of the possible candidates to avoid a promising, but untested treatment. At the same time, physicians who become excessively convinced on the basis of such appropriately designed pilot studies would not be able to escape by using the argu-

ment that they would find subsequent randomization to be unethical.

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MORE ON CORONARY BYPASS SURGERY—III

One point I would like to raise concerns the absolute acceptance of a left main coronary lesion as an indication for surgery. The only study that has explored this in a controlled manner is the Veterans Administration study. Criticism on this point has recently been published by Graham.[1]

An argument can be made that not all of the patients treated medically were receiving propranolol, none were receiving sulfinpyrazone (later shown to reduce the incidence of sudden death)[2] and all were taken care of in a clinic setting as provided by VA institutions. One could suggest that caring for patients in a private practice setting might favorably influence prognosis. In addition, subsets of patients with left main coronary artery disease have been described.[3,4] Such patients should be further categorized as to whether the left main artery is narrowed by 50 to 70 percent, 70 to 90 percent or 90 percent or greater, the status of the right coronary artery and of the left ventricle, as well as other clinical and noninvasive indicators.

It would appear that medical management has advanced significantly since the VA study and that further randomized trials of selected patients with left main coronary artery disease might very well be warranted.

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MORE ON CORONARY BYPASS SURGERY—IV

We take issue with the statement by Hultgren et al. that "improved patient selection" is an important factor in the decrease in operative mortality for coronary bypass surgery seen during the last 8 years.

Before 1974, patients with a systolic ejection fraction of less than 0.30, recent myocardial infarction, unstable angina, poorly visualized vessels beyond obstructions and chronic renal disease (creatinine clearance less than 30 ml/min) were generally excluded from surgery or experienced an increased mortality rate. All of these patient groups are now operated upon with a 1 percent, 30 day operative mortality rate.[1] This practice pattern and these results in two settings (Penn State's Milton S. Hershey Medical Center in Hershey, Pennsylvania, and the University of Texas Medical Branch in Galveston, Texas), best described as "cottage industries" compared with the Cleveland Clinic, contrast sharply with the exclusion of all but low risk candidates from the Veterans Administration Cooperative Study. To believe that in 1978, only lower risk patients are being operated upon, as the VA study group obviously does, further illustrates their separation from the main stream of cardiological and surgical experience.

We also fail to see how Braunwald's ability to find two reports of operative mortality as poor as those reported in the VA study answers Loop's complaint that a clinical trial should be designated to study the operation, not the surgeon. It doesn't take a prospective study to determine that any act of skill can be performed poorly. The fact that a few VA hospitals (for example, that of Hines) contributed a majority of the patients and that their results are well within the national average, is also "bypassed." Equally important is the knowledge that many VA hospitals did coronary bypass surgery only occasionally with mortality and complication rates far above the national average. In short, the means in the VA study are less interesting than the ranges, which the apologists never mention.

Finally, the sensational headlines generated by the original report and editorials in *The New England Journal of Medicine*[2,3] and the subsequent interviews that portrayed cardiologists and cardiothoracic surgeons practically at battle over indications for bypass surgery can hardly be passed off as the "sober analysis" characterized by Braunwald.[2]

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RETROGRADE CROSSING OF AORTIC BJORK-SHILEY PROSTHESIS

Karsh et al.[1] report on the safety and efficacy of retrograde left ventricular catheterization in patients with aortic valve prostheses, and record their experience with 27 patients with either a Starr-Edwards or a Bjork-Shiley prosthesis. No mention is made of how many patients had each prosthesis. Their Figure 3 shows a catheter crossing a Starr-Edwards valve prosthesis, showing little disturbance of the poppet while the catheter is across the valve; however, this frame was taken during systole and would therefore not be expected to show interference with the diastolic closing mechanism of the valve.

We strongly advise caution regarding the retrograde crossing of aortic Bjork-Shiley prostheses. Unlike the Starr-

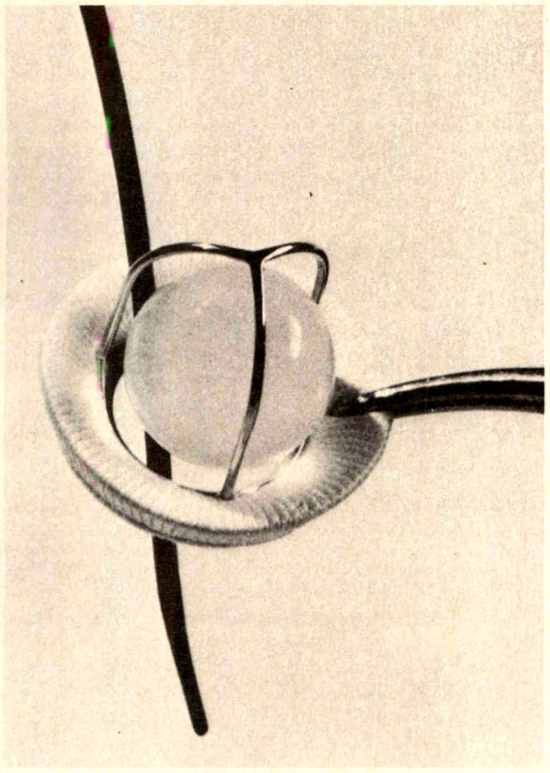


FIGURE 1. Starr-Edwards prosthesis with catheter placed across it.

Edwards prosthesis, which is symmetric, and in which placing a catheter across it produces relatively minor unseating of the spherical poppet (Fig. 1), the Bjork-Shiley valve is asymmetric, with a large strut holding the disc on the ventricular side and a smaller strut checking the opening of the disc on the aortic side. A catheter placed across the large opening (Fig. 2, top) will likely produce minor interference of disc seating and, therefore, presumably little hemodynamic disturbance. However, a catheter placed across the small strut will lock the disc in a wide open position and produce acute, massive aortic regurgitation (Fig. 2, bottom).

Figure 3 shows the sequence of hemodynamic recordings in a patient with an aortic Bjork-Shiley prosthesis studied because of suspected paravalve regurgitation. Simultaneous pulmonary arterial wedge pressure and aortic pressure tracings were obtained before the valve was crossed; the pulmonary wedge pressure was slightly elevated (mean pressure 18 mm Hg, panel A). Because the patient was believed to have a paravalve aortic leak, the aortic no. 8F National Institutes of Health catheter was advanced gently and entered the left ventricular cavity with ease. No gradient was observed between the pulmonary wedge and the left ventricular diastolic pressure. A few minutes later the patient complained of chest discomfort, and it was noted that the left ventricular end-diastolic pressure had risen from 22 to 52 mm Hg, and the pulmonary wedge pressure from 18 to 45 mm Hg. The catheter was immediately withdrawn into the aorta (panel B). This resulted in a prompt clearance of symptoms and return to the previous hemodynamic state (panel C). An aortogram demonstrated moderate regurgitation around the prosthetic valve; the catheterization was completed without further difficulty. We interpret the serious hemodynamic disturbance demonstrated to the induction of acute, severe aortic regurgitation by the catheter, possibly through the mechanism illustrated in Figure 3. The valve disc used had no radiopaque markers; therefore, serious interference with prosthetic disc seating was impossible to identify. The newer models of the Bjork-Shiley valve have incorporated a radiopaque ring into the disc, making possible fluoroscopic identification of disc motion and position, which may help in avoiding this problem.

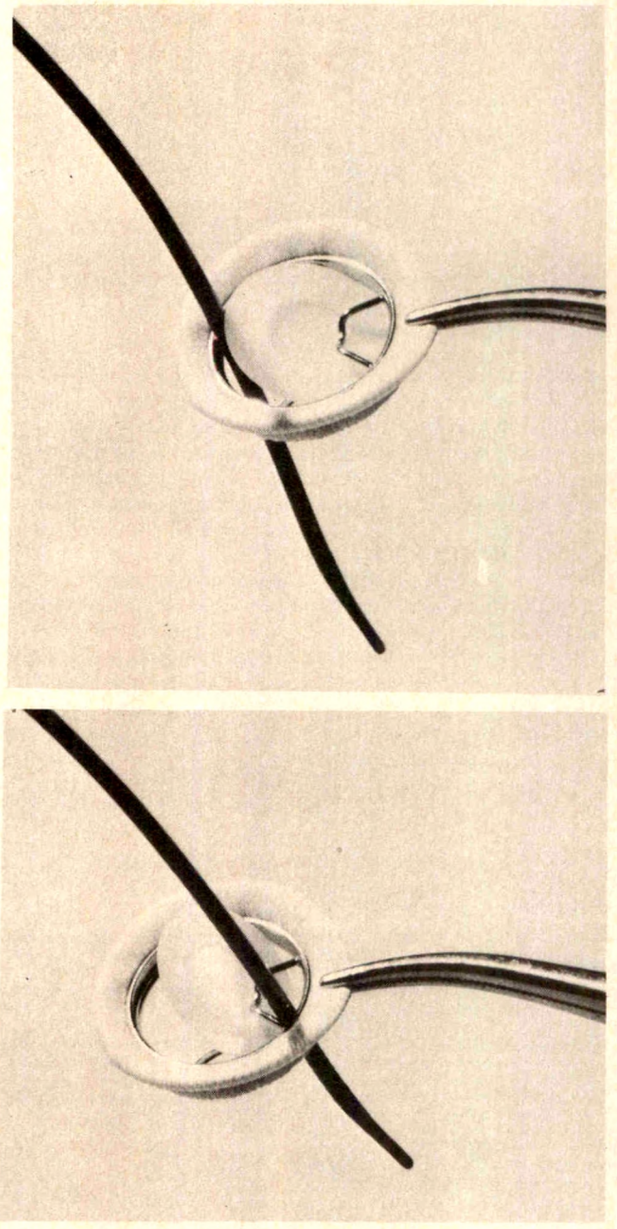


FIGURE 2. Bjork-Shiley prosthesis with catheter placed across large opening (**top**) and across the small strut (**bottom**).

Some postoperative evaluation studies of Starr-Edwards valves[2,3] have essentially agreed with the findings of Karsh et al.; others [4]have demonstrated consistently significant increases in left ventricular end-diastolic pressure after retrograde passage of the catheter through the valve, presumably because of induced aortic regurgitation. Thus, detailed as-

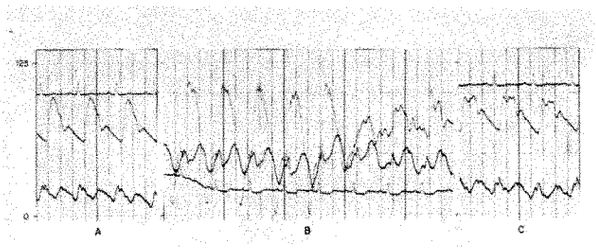


FIGURE 3. Pressure tracings in a patient with a Bjork-Shiley prosthesis. See text.

sessment of left ventricular function and the assessment of effective valve orifice area in cases with suspected prosthetic obstruction may be altered by this technique.

We conclude that retrograde catheterization of the aortic Starr-Edwards prosthesis may be an acceptable, although less than ideal, method but would strongly recommend against attempting retrograde catheterization of the left ventricle across an aortic Bjork-Shiley prosthesis because of the likelihood of producing acute, massive aortic regurgitation through serious interference with the disc-closing mechanism.

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REPLY

Falicov and Walsh have made the useful point that, because of its construction, a Bjork-Shiley prosthetic valve is more susceptible to interference with function during the period of time a catheter is traversing it than is a Starr-Edwards prosthesis. Our experience included a total of 27 patients, 5 of whom had a Bjork-Shiley prosthesis. We did not note any substantially increased interference with function with the latter prosthesis, but Falicov and Walsh have ignored a critical point described in our methods section. This is that we utilized either Sones or Shirey catheters, both of which taper to a no. 5F tip, or no. 5F polyethylene catheters primarily for our studies. Thus, all prostheses were crossed with smaller catheters than those used by Falicov and Walsh.

In addition, they comment on our Figure 3, which shows no interference with movement of a Starr-Edwards poppet in systole. As noted in our text (on page 895), the Starr-Edwards poppets did not appear to seat completely in diastole with catheters crossing the valve. However, "hemodynamically detectable aortic regurgitation, as estimated from pressure changes on catheter pullback, was observed in only 3 patients." Examination of the pressure tracings submitted by Falicov and Walsh testifies to interference with both systolic and diastolic excursion of the Bjork-Shiley prosthesis. There are elevation of left ventricular systolic and diastolic pressures and depression of both systolic and diastolic aortic pressures in the first two complexes recorded during pullback of the catheter through the valve. Once again, it must be pointed out that they used a no. 8F catheter.

We believe that their letter does point out a useful word of caution in dealing with retrograde catheterization of Bjork-Shiley prostheses. However, this problem should be at least partially avoided by utilizing smaller catheters.

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SIGNIFICANCE OF CHEST PAIN DURING TREADMILL EXERCISE

The paper by Cole and Ellestad[1] on the significance of chest pain during treadmill exercise contains potentially important information, but we think that several points should be clarified.

The 7 year mortality rate was only 27 percent in the patients with both an abnormal electrocardiogram and typical angina pectoris during exercise; according to previous findings and the reported data,[1] such patients are very likely to have significant coronary artery disease, and the expected mortality would be much greater than that observed (Bruschke et al.[2] reported a 7 percent annual mortality rate). The inclusion of an undefined number of women could contribute to these findings but is not likely to be the only explanation.

The true positive rate for women with pain and electrocardiographic abnormalities during exercise was only 17 percent; although it is widely recognized that the diagnosis of coronary artery disease is not easy to establish in women, the reported figure is incredibly low and raises questions about the definition of angina pectoris in that study.

We[3] recently reported that in patients with suspected coronary artery disease, the history taken before the exercise test was of great diagnostic value and that, among the patients with a typical history of angina pectoris, the occurrence of chest pain during the exercise test itself did not add much information. All patients described by Cole and Ellestad were certainly carefully questioned before the exercise test and it would be very important to know how this information relates to prognosis. It would indeed be unfair to attribute to exercise testing a diagnostic and prognostic value that is probably already present in the history.

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REPLY

The true positive rate for women with angina during the treadmill stress test was 71 percent (17 percent was a typographical error). This result is identical to that of the report of Detry et al. (their Ref 3).

In our study, the patients included those "referred for confirmation of suspected coronary artery disease, for quantification of the degree of known coronary artery disease or for a routine screening test as part of their annual physical examination." The work reported by Bruschke cited a 5 year overall mortality rate of 34.4 percent with angiographic correlation. As noted, some of their patients died within weeks to months of their angiograms. No correlations with exercise testing of this population were found in their manuscript. We have yet to understand why some authors wish to make the data from one population of patients "fit" with those of another.

In both Detry's study and ours, about one third of the patients had typical angina during exercise testing. If the patient had angina during the test, the sensitivity of the test was increased in both men (91 percent) and women (71 percent). The main thrust of our study indicated that a history alone would not have sufficed. Subjects with angina induced by a light work load (1 to 3 minutes of testing, 4 METS) had twice the frequency of coronary events (progression of angina, myocardial infarction, coronary death) as that of patients with angina induced by a heavy work load (7 minutes of exercise, 9 METS). As we pointed out in our article, "the difference in results of other studies may well be due to inherent differences in patient selection because our study, by design, included many subjects known or highly likely to have advanced coronary artery disease as well as many believed to be perfectly normal."

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CARDIOPULMONARY RESUSCITATION AFTER AGE 65

In my opinion, the usual 20 to 30 minute attempt at cardiopulmonary resuscitation is maleficent for many patients over age 65. I know from a personal survey that resuscitation after an unobserved cardiac arrest is not desired by the majority of doctors over age 60. I have also ascertained that after a true cardiopulmonary arrest, even in a coronary care unit, nearly 50 percent of practicing internists 65 years or older do not wish more than a 5 minute attempt at resuscitation.

Among 87 patients over age 65 there were a total of 96 "code-blue" alerts in a 2 year period at Peninsula Hospital and Medical Center, Burlingame, California. Forty-one of these patients were pronounced dead at the end of the attempted resuscitation. Among those resuscitated were three whose own doctor believed that their quality of life was only fair after they left the hospital. Fourteen patients had excellent results. Of these, 11 were returned to a viable heart rate and rhythm in 5 minutes or less.

Central to the issue of this letter were the 29 patients who, as the result of heroic attempts at resuscitation, ranging from 10 to 60 minutes and averaging 30 minutes, experienced a prolongation of 1/2 hour to 1 month of their act of dying! I consider this a summum malum result and believe that most patients and their families would consider this maleficent.

In a study done in 1976 at three hospitals in Nurnberg,[1] of 239 patients over age 60 who were resuscitated, only 9 were alive 6 months later. Seven of these nine, when questioned, would not agree to another resuscitation effort.

The vast majority of my patients over 65 tell me that (1) they do not dread death, and hope that theirs will be sudden; and (2) they do fear incarceration in a nursing home or total dependence on others.

Therefore, I recommend some method, such as a "modified living will," [2] to give our sapient patients over age 65 an opportunity to indicate in advance their wishes regarding resuscitation efforts lasting more than 5 minutes. For those patients over 65 who have not clearly indicated their wishes I urge that the following suggestions be considered as medically acceptable alternatives to aggressive resuscitation efforts: (1) positively no cardiopulmonary resuscitation for any *unobserved* cardiac arrest, and (2) 5 minutes' maximal cardiopulmonary resuscitation to reestablish a viable heart rhythm in a patient with any instantly observed and immediately treated cardiac arrest.

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AMERICAN COLLEGE OF CARDIOLOGY NEWS

The following five abstracts are from the winning entries in the Young Investigators' Awards Competition, 28th Annual Scientific Session, the American College of Cardiology, March 11–15, 1979, Miami Beach, Florida.

First Award

A BIOLOGICAL MODEL OF PARASYSTOLE. J. Jalife, M.D., and G.K. Moe, M.D., Ph.D., F.A.C.C., Masonic Med. Res. Lab., Utica, NY 13503.

The electrotonic interactions of a parasystolic pacemaker with ventricular responses to the normal pacemaker across an area of depressed excitability were simulated in a model consisting of strands of canine Purkinje fibers mounted in a sucrose gap preparation. Experiments were conducted to study the patterns of ectopic activity that result from entrainment of the "ectopic" pacemaker (EP) on one side of the sucrose gap, by evoked responses (SN) in the other side of the gap. When one-way conduction ("entrance block") was established, manipulations of the SN frequency and of the impedance between the two outer chambers resulted in periods of silence, concealed or manifest bigeminy, trigeminy and quadrigeminy, and periods of more complex patterns of group beating as the entrainment ratios changed. The results confirm the predictions of the previously described mathematical model that these patterns depend upon the magnitude of the electrotonic influence of SN on the EP cycle length and also upon the ratio of the intrinsic frequencies. These studies should help to distinguish between reentrant and parasystolic mechanisms in clinical arrhythmias.

Second Award

PATHOGENESIS OF MALIGNANT HYPERTENSION PRODUCED BY MILD PROGRESSIVE RENAL ARTERY STENOSIS

Victor J. Dzau, MD; Seymour Rosen, MD; A. Clifford Barger, MD, Harvard Medical School, Boston, MA

To simulate development of human renovascular hypertension, mild daily progressive renal artery constriction (PRAC) was substituted for single stage constriction in the one-kidney Goldblatt dog. Surprisingly, all 11 dogs so treated developed malignant hypertension (MH) which persisted despite release of constriction. To induce hypertension, fluid was injected into an inflatable RA cuff to lower renal perfusion pressure (RPP) by 5 mmHg below preconstriction pressure each day for 10-14 days. However, as MAP rose, RPF returned toward control in hours. Thus, daily PRAC did not lead to sustained RA hypotension; in fact, by the 7th day RPP began to rise above control. With MH, MAP increased from 107 ± 4 to 204 ± 11 mmHg while RPP increased to 130 ± 9 mmHg; plasma renin activity (PRA) rose from 1.0 ± 0.1 to 30 ± 5 ng A^I/ml/hr. Plasma aldosterone concentration (PAC) parallelled PRA. I.V. administration of Teprotide (CEI) lowered MAP to control. Renal blood flow (RBF) and filtration rate (GFR) fell below control within 2-3 days and progressively declined with repeated PRAC. Intrarenal resistance (RR) was markedly elevated (>10 fold during MH) but was dramatically reduced with intrarenal blockade of converting enzyme. Despite cuff release, RBF and GFR continued to decline while PRA increased further. Initial moderate salt and water retention was followed by a marked natriuresis and diuresis (N and D) leading to weight loss, plasma volume (PV) contraction and hemoconcentration. Thus, mild PRAC without sustained RA hypotension leads to a vicious cycle with a progressive rise in PRA, increased RR, N and D with resultant fall in PV, - a process terminating in MH with severe vascular damage.

Honorable Mention

INTERACTION BETWEEN CARDIAC AND SINOAORTIC BARORECEPTORS IN THE CONTROL OF EFFERENT CARDIAC SYMPATHETIC NERVE ACTIVITY DURING MYOCARDIAL ISCHEMIA IN DOGS. Robert B. Felder, M.D. and Marc D. Thames, M.D., University of Iowa, Iowa City, Iowa 52242.

The purpose of this study was to determine the relative influence of arterial baroreceptors(BR)and of cardiac receptors with vagal afferents and with sympathetic afferents on efferent cardiac sympathetic nerve activity(CSNA) during coronary artery occlusion(CAO). Changes in heart rate(HR in beats/min), arterial pressure(AP in mmHg), and integrated CSNA(% change from control; recorded from the cut central end of the left ventral ansa subclavia)were determined during transient(90 sec) circumflex (Cx) and anterior descending(LAD)CAO before and after vagotomy (V). Before V dogs with carotid and aortic BR intact showed a similar increase(mean±SE)in CSNA during Cx(7±1%)and LAD (7±3%)occlusions in spite of a significantly greater fall in AP during Cx(-18±1)than during LAD(-7±2)CAO. HR did not change during these occlusions. During Cx CAO dogs with sinoaortic denervation had decreases in CSNA(-17± 2%), AP(-50±4 mmHg), and HR(-17±3 beats/min). In these dogs LAD occlusion resulted in a smaller decrease in AP (-14±3 mmHg)with no change in CSNA or HR. In dogs with sinoaortic denervation and vagotomy Cx and LAD occlusion resulted in similar decreases in AP(-29±3 and -21±3 mmHg, respectively), and small and inconsistent changes in HR and CSNA. We conclude that cardiac receptors with vagal afferents exert an inhibitory influence on CSNA during myocardial ischemia, and that this influence limits the arterial BR mediated increases in CSNA resulting from ischemia-induced hypotension. Small changes in CSNA during CAO with vagi and BR afferents sectioned suggest that in the dog cardiac receptors with sympathetic afferents do not exert a major influence on the sympathetic outflow to the heart during myocardial ischemia.

Honorable Mention

EFFECTS OF RETROGRADE SYSTOLIC STRETCH OF ISCHEMIC MYOCARDIUM

J. David Ogilby; Lorentz Preysz; Carl S. Apstein, MD, FACC Cardiac Muscle Research Lab, Boston University, Boston, MA

To assess the effects of the paradoxical or retrograde systolic stretch which is imposed on fibers in ischemic regions, isolated globally ischemic rabbit hearts (balloon in LV) were paced at 180/min and subjected to 90 min of ischemia (I) at 37°C with or without imposed repetitive 180/min systolic expansion (SE) of the LV balloon to a level which duplicated pre-I systolic LV pressure. Post-I recovery was assessed for 60 min. With severe I (<1% of control coronary flow) active contractions ceased within 2-3 min. Without SE (n=6), 40±6mm Hg contracture occurred during I; SE (n=6), completely prevented contracture during I. Post-I recovery of developed pressure without SE was 27±4% vs 63±3% with SE (P<0.001); recovery of dP/dt without SE was 34±5% vs 79±6% with SE (P<0.001). For SE vs no SE, post-I ATP was 9.6±0.7 vs 5.5±0.4mM/gm (P<0.001) and CP was 36±4 vs 19±2mM/gm (P<0.01), indicating that SE and prevention of contracture preserved high energy phosphate levels. During moderate I (13% of control flow) LV contractile function of 26% of the pre-I developed pressure continued for 90 min of I. Thus, in this moderate I group, SE caused retrograde stretch in opposition to actively contracting ischemic muscle. No contracture occurred during moderate I in either group. For SE (n=6) vs no SE (n=6) post-I developed pressure recovered to 73±4% vs 87±2% (P<0.005) and dP/dt recovered to 78±5 vs 98±4% (P< 0.01). Thus, in the absence of active contractility (severe I), SE was beneficial, prevented contracture, preserved tissue high energy phosphates and improved post-I contractile function. However, when SE was in opposition

to active shortening (moderate I), the effect was deleterious and post-I contractile function was decreased.

Honorable Mention

EFFECTS OF TRAINING ON LEFT VENTRICULAR FUNCTION IN NORMAL SUBJECTS: A LONGITUDINAL STUDY.
Stephen K. Rerych, MD; Peter M. Scholz, MD; David C. Sabiston, Jr., MD, FACC; Robert H. Jones, MD, FACC; Duke University Medical Center, Durham, North Carolina

Radionuclide angiocardiography provides accurate hemodynamic information during maximal exercise in erect subjects. Cardiac function was studied by this noninvasive technique in 12 male and 6 female college athletes before (BT) and after (AT) 6 months of aquatic training. Rest (R) and maximal exercise (E) measurements of heart rate (HR), left ventricular ejection fraction (EF), end-diastolic volume (EDV), cardiac output (CO) and total body blood volume (TBV) were determined from first pass and equilibrium precordial counting techniques.

	HR (b/min)	EF (%)	EDV (ml)	CO (l/min)	TBV (L)
BT-R	74±11	73±6	133±35	6.9±1.1	8.7±0.8
AT-R	61±7	67±7	167±40	6.7±1.0	11.4±2.2
BT-E	185±10	87±4	166±34	25.5±5.7	8.0±0.9
AT-E	181±14	86±5	204±39	32.0±8.7	10.8±2.3

TBV increased AT ($P<0.03$). Although CO was similar at rest BT and AT, a decrease in HR ($P<10^{-4}$) and EF ($P<10^{-3}$) was associated with an increase in EDV ($P<10^{-5}$). CO at E increased ($P<0.02$) AT because of an increased EDV ($P<10^{-4}$) with a constant HR and EF. Individual variation was observed in the performance level achieved and the maximum CO at E AT of 56.6 l/min was attained by an Olympic athlete. Training appears to enhance cardiac performance primarily by inducing cardiac dilatation.

NEW MEMBERS

The following individuals were elected to membership in the American College of Cardiology on February 1, 1979 in the category indicated.

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SCHWEIGER, Marc J., MD, Springfield, MA
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SULLIVAN, Henry J., MD, Maywood, IL
SUMA, Kozo, M.D., PhD, Tokyo, Japan
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29th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY

Houston, Texas **March 9–13, 1980**

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee
for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

MAY 1979 THROUGH SEPTEMBER 1979

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

MAY 3-5 — **Critical Care Cardiology.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. Golden Gateway Holiday Inn, San Francisco, CA

MAY 3-5 — **Ischemic Heart Disease.** James E. Dalen, FACC, director and Thomas J. Ryan, FACC, Thomas W. Smith, FACC, Herbert J. Levine, FACC and Joseph S. Alpert, FACC, co-directors. Copley Plaza Hotel, Boston, MA

MAY 9-11 — **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, Antonio C. de Leon, Jr., FACC, and John F. Stapleton, co-directors. Georgetown University Medical Center, Washington, DC

MAY 18-21 — **A Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC, and Leo Schamroth, FACC, directors. Sheraton Sand Key Hotel, Clearwater Beach, FL

MAY 21-24 — **Coronary Atherosclerotic Heart Disease—1979.** J. Willis Hurst FACC, director and Robert C. Schlant, FACC, co-director. Colony Square Hotel, Atlanta, GA

JUNE 6-10 — **Cardiac Auscultation Workshops.** Jules Constant, FACC, director. Niagara Hilton Hotel, Niagara Falls, NY

JUNE 13-16 — **Sixth Annual Symposium. Clinical Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** Arthur D. Hagan, FACC, director and William F. Friedman, FACC and Walter V. R. Vieweg, FACC, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

JUNE 21-23 — **Medical and Surgical Management of Coronary Artery Disease.** M. Leo Hughes, Jr., FACC, director and Robert C. K. Riggins and Richard P. Anderson, co-directors. Virginia Mason Medical Center, Seattle, WA

AUG. 25-27 — **Tutorials in the Tetons: Cardiac Emergencies (Fifth Annual).** Robert S. Eliot, FACC and Alan D. Forker, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Moran, WY

SEPT. 10-13 — **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC, director and Charles Fisch, FACC, co-director. Wishard Memorial Hospital, Indiana University Medical Center, Indianapolis, IN

SEPT. 10-13 — **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Fairmont Hotel, San Francisco, CA

SEPT. 17-19 — **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya, James C. Dillon, FACC and Arthur E. Weyman, FACC, codirectors. Indianapolis Hilton Hotel, Indianapolis, IN

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

MAY 1979 THROUGH JULY 1979

Month/Dates	Course Director	Title of Program
May 3–5	Daniel S. Berman, MD, FACC	**Nuclear Cardiology**
May 7–9	Leonard S. Dreifus, MD, FACC	**Cardiac Rehabilitation: Principles and Techniques**
May 14–16	Louis Lemberg, MD, FACC	**CCU Update for Nursing Supervisors**
May 21–23	James E. Doherty, III, MD, FACC	**Clinical Cardiovascular Pharmacology: Rational Approach to Drug Therapy**
May 24–25	Joseph K. Perloff, MD, FACC	**The Fundamentals of Echocardiography: A Practical Course for Clinicians**
May 30–June 1	Ira H. Gessner, MD, FACC	**The Principles of Pediatric Cardiology: A Fundamental Approach**
June 11–13	Shahbudin H. Rahimtoola, MD, FACC	**Valvular Heart Disease**
June 20–22	Michael S. Gordon, MD, FACC	**Cardiac Auscultation**
June 25–27	Sylvan L. Weinberg, MD, FACC	**CCU Update for Nursing Supervisors**
July 5–7	G. Charles Oliver, MD, FACC	**Ambulatory Monitoring and Sudden Death**

AMERICAN COLLEGE OF CARDIOLOGY

Announces . . .

AFFILIATE IN TRAINING MEMBERSHIP

For Physicians in Cardiovascular Related Training Programs

Candidates for this membership category must be current full-time trainees in a recognized cardiovascular (adult, pediatric, surgical) related program in fulfillment of requirements for admission to a subspecialty board examination which holds membership in the American Board of Medical Specialties. Upon completion of training and in order to maintain an affiliation with the College, the members are encouraged to apply to the Credentials Committee for status in one of the other three membership categories.

The application for Affiliate in Training must be signed by the Director of the applicant's training program and two sponsors, both of whom must be Fellows of the College. One of the sponsors may be the Director of the training program, provided he is a Fellow of the College. The annual dues for an Affiliate in Training are $25.00.

Advantages to the Affiliate in Training

1. Subscription to *The American Journal of Cardiology*, the official journal of the College.
2. Reduced fees for all educational programs of the College.
3. Preference for enrollment in programs sponsored by the College with a limited registration.
4. Receipt of the quarterly publication, *Cardiology*, the newsletter of the College.
5. Participation in all affairs of the College as a member rather than as a guest of the College.

Those desiring an application form should write to Ms. Margaret E. Coffey, Director, Membership Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

INSTRUCTIONS FOR AUTHORS

The editors of THE AMERICAN JOURNAL OF CARDIOLOGY welcome concise articles devoted to cardiovascular disease. Articles must be contributed solely to THE AMERICAN JOURNAL OF CARDIOLOGY and become the property of the Publisher. The Publisher reserves copyright and renewal on all published material, and such material may not be reproduced in any form without the written permission of the Publisher. Statements in articles are the responsibility of the authors. Authors will assist the editors in the prompt processing of manuscripts if these instructions are followed:

THE WHOLE PAPER

- Address manuscript to Managing Editor, American Journal of Cardiology, 666 Fifth Ave., New York, NY 10019.
- Submit two copies of all elements of the article: text, references, legends, tables and figures.
- Arrange the paper in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- Number all pages in above sequence, beginning with title page as 1, abstract as 2, etc.
- Type all matter: (1) on 8½ × 11 opaque white bond paper; (2) in duplicate; (3) on one side of each sheet only; (4) double-space; (5) leave wide margins, all four sides.

THE TITLE PAGE

- Include first names, degrees and, where applicable, FACC for all authors.
- Provide a short running title of 3 to 6 words.
- Insert at bottom: name and address of institution from which work originated plus information about grants.
- Add at bottom the phrase "Address for reprints: . . ." followed by full name and address with zip code.

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- Limit words as follows: 100 to 250 words for major articles; 50 to 100 words for case reports.
- Add at end of abstract: list of 2 to 6 key words and subjects for indexing.

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- Type in duplicate; double-space.
- Do not use abbreviations such as SVC, WPW: write out superior vena cava, Wolff-Parkinson-White.
- Abbreviate measurements (mm, kcal and the like) as recommended in the Style Manual for Biological Journals, American Institute of Biological Sciences, 3900 Wisconsin Avenue, N.W., Washington, D. C.
- Cite in numerical order every reference, figure and table. (Order of mention in text determines the number given to each.)
- Place acknowledgments at end of text, before references.

THE REFERENCES

- Type in duplicate; double-space.
- Number the references in order in which they are mentioned in text.
- Provide concluding page numbers for all journal references and specific page numbers for all book references. Indicate all abstracts by the abbreviation (abstr).
- Follow the general arrangement, abbreviations and punctuation styles shown below.

THE FIGURE LEGENDS

- Start at top of new page.
- Type in duplicate; double-space.
- Number pages in sequence after last page of references.
- Identify at the end of each legend and in alphabetical order all abbreviations in the figure described.

THE TABLES

- Start each table at top of new page.
- Type in duplicate, double-space.
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THE FIGURES

- Submit 2 glossy prints (not originals) of each photo and drawing.
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Examples of Styles of References

For periodicals, follow INDEX MEDICUS, listing *all* authors:

31. Vismara LA, Vera Z, Miller RR, Mason DT: Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. Am J Cardiol 39:1027–1034, 1977

(Author: please note that no periods are used after authors' initials.)

For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

For books (with identical author and editor):

36. Berne E: Principles of Group Treatment. New York, Oxford University Press, 1966, p 26

(Author: all book references should have specific page numbers.)

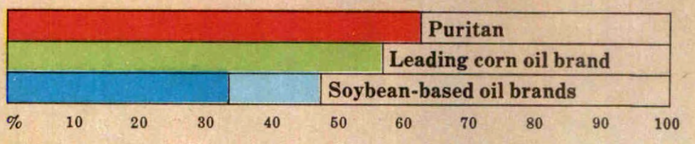
Puritan Oil® is superior in polyunsaturates to corn oil*



A practical adjunct in serum cholesterol control

Puritan is the first major cooking oil made principally from highly polyunsaturated sunflower oil. The sunflower oil gives Puritan an edge in polyunsaturate levels over leading corn and soybean-based oils.

*** A comparison of polyunsaturate levels of major brands**



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The sunflower oil also makes Puritan light tasting. In taste tests conducted with Puritan and corn oil, Puritan Oil was selected as lighter tasting by homemakers. It contributes to an appealing diet for patients and family and thus helps enhance sustained compliance with your cholesterol management program.

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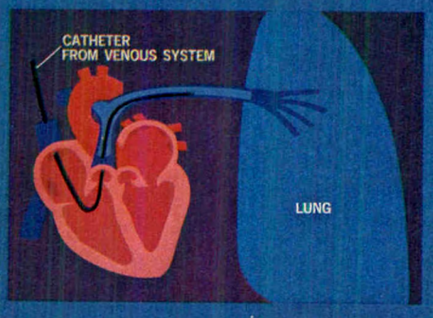


The nutrition department of a major university has published the results of a study[1] that evaluated a dietary serum-cholesterol-reducing program which included Puritan Oil. The study was conducted in a family situation—entire families used Puritan as part of a total serum-cholesterol-reducing diet. The data showed significant decreases in serum cholesterol levels among all participating groups. These lowered levels were reached within 10 days, and were maintained throughout the diet modification period.

Reference: 1. Witchi, J.C. et al., *J. Am. Dietetic Assoc. 72:* 384, 1978.

New cardiac catheterization studies demonstrate prolonged changes for over 5 hours in cardiac hemodynamics with PERITRATE® 40-mg ORAL TABLET

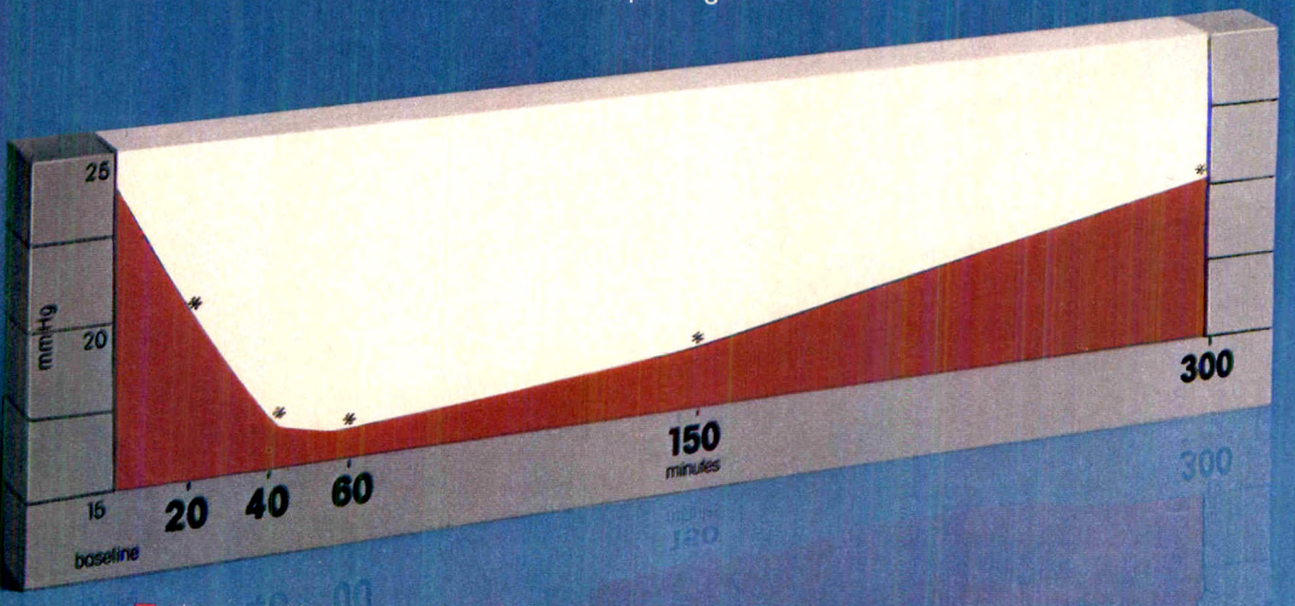
(pentaerythritol tetranitrate)



In a randomized double-blind study of catheterized patients with congestive heart failure, Peritrate 40 mg demonstrated marked changes in a variety of hemodynamic parameters with no change in heart rate.[1]

A marked reduction in PRELOAD: Peritrate reduced pulmonary arterial wedge pressure for over 300 minutes. The maximum reduction was 37%. Pulmonary arterial mean pressure was also reduced for over 300 minutes. These manifestations of reduced PRELOAD resulted from an increase in venous capacitance leading to a reduction in left ventricular end-diastolic volume and pressure. The observed reduction in pulmonary wedge pressure indicates marked preload reduction.

Peritrate effects prolonged for 5 hours



pulmonary arterial wedge pressure (preload)
*Statistically significant at the 5% level.

A reduction in AFTERLOAD: A significant reduction of arterial blood pressure, correlating with reduced AFTERLOAD, was maintained for over 300 minutes.[1]

Reduction in blood pressure for 5 hours

parameter	before Peritrate n=12	60 minutes after Peritrate n=12	150 minutes after Peritrate n=12	300 minutes after Peritrate n=8
blood pressure (mmHg) systolic	122.6	116.7*	116.9	116.8*
diastolic	68.7	63.4*	61.3*	61.0*

*Statistically significant at the 5% level.

Peritrate actions observed

- Activity was prolonged for at least 5 hours.
- PRELOAD and AFTERLOAD showed a marked reduction lasting at least 5 hours.

1. Klein RC, Amsterdam EA, Pratt C, et al: Sustained reduction of elevated left ventricular filling pressure in cardiac failure by oral, long-acting nitrate therapy. Presented at The American Federation for Clinical Research, San Francisco, Calif, April 29-May 1, 1978.

Please see following page for brief summary of prescribing information.

Conclusions

1. The prolonged reduction in preload and afterload reduces the amount of energy expended and oxygen consumed by the heart. This reduction in oxygen demand should relieve or prevent angina.
2. Provides a smooth onset of action without tachycardia. Unwanted effects are rare, and patient compliance is excellent.

PERITRATE® 40 mg
(pentaerythritol tetranitrate)

Warner/Chilcott
Division,
Warner-Lambert Company,
Morris Plains, New Jersey 07950

Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) **80 mg**
Peritrate®
(pentaerythritol tetranitrate) **40 mg**
Peritrate®
(pentaerythritol tetranitrate) **20 mg**
Peritrate®
(pentaerythritol tetranitrate) **10 mg**

CAUTION: Federal law prohibits dispensing without prescription.

Description: Each tablet of Peritrate SA Sustained Action contains pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature.

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).

Peritrate (pentaerythritol tetranitrate) 40 mg—pink scored tablets in bottles of 100 (N 0047-0008-51).

Peritrate (pentaerythritol tetranitrate) 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also unit dose, package of 10 x 10 strips (N 0047-0001-11).

Peritrate (pentaerythritol tetranitrate) 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

STORE BETWEEN 59° and 86° F [15° and 30° C].

Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.

Full information is available on request.

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Division,
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PE-GP-82

ALDACTONE®
(spironolactone) 25 mg. tablets

WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

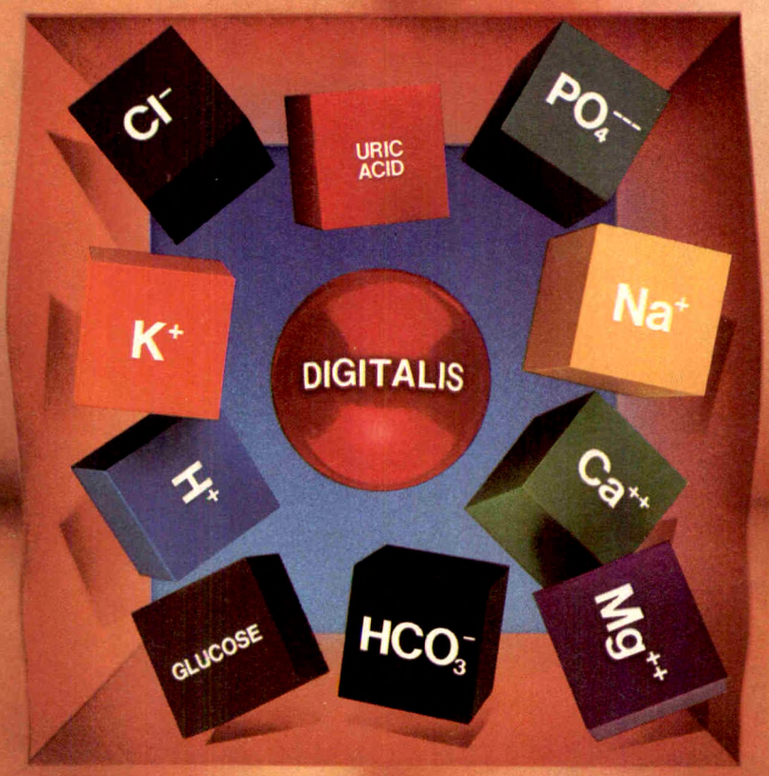
For hypokalemia: 25 to 100 mg. daily in divided doses.

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817

The delicate balance during treatment of CHF



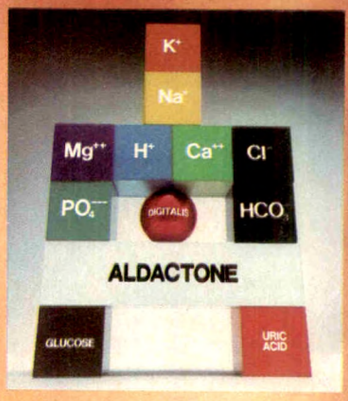
Electrolyte imbalance is often a problem during digitalis therapy and most diuretics can worsen the problem. With both the thiazides and furosemide, fluid and electrolyte imbalance may lead to digitalis toxicity.

Aldactone for concomitant digitalis/diuretic therapy.

Aldactone® (spironolactone) provides gradual and sustained diuresis and, through a unique mechanism, helps prevent hypokalemia with limited risk of hyperkalemia. *Plus* . . . Aldactone does not adversely affect serum calcium, magnesium, and uric acid levels nor alter glucose tolerance.

Limitations to consider.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Thus Aldactone should be prescribed only when other measures are considered inadequate or inappropriate. (See boxed warning and *Warnings* section of Aldactone prescribing information, a brief summary of which appears on the facing page.)



SEARLE

Aldactone®

(spironolactone) 25-mg. tablets

The diuretic that helps maintain the delicate balance of electrolytes . . . when other measures are considered inadequate or inappropriate.

Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the facing page.

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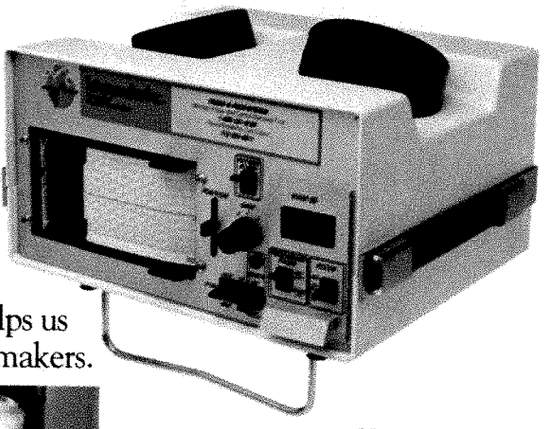
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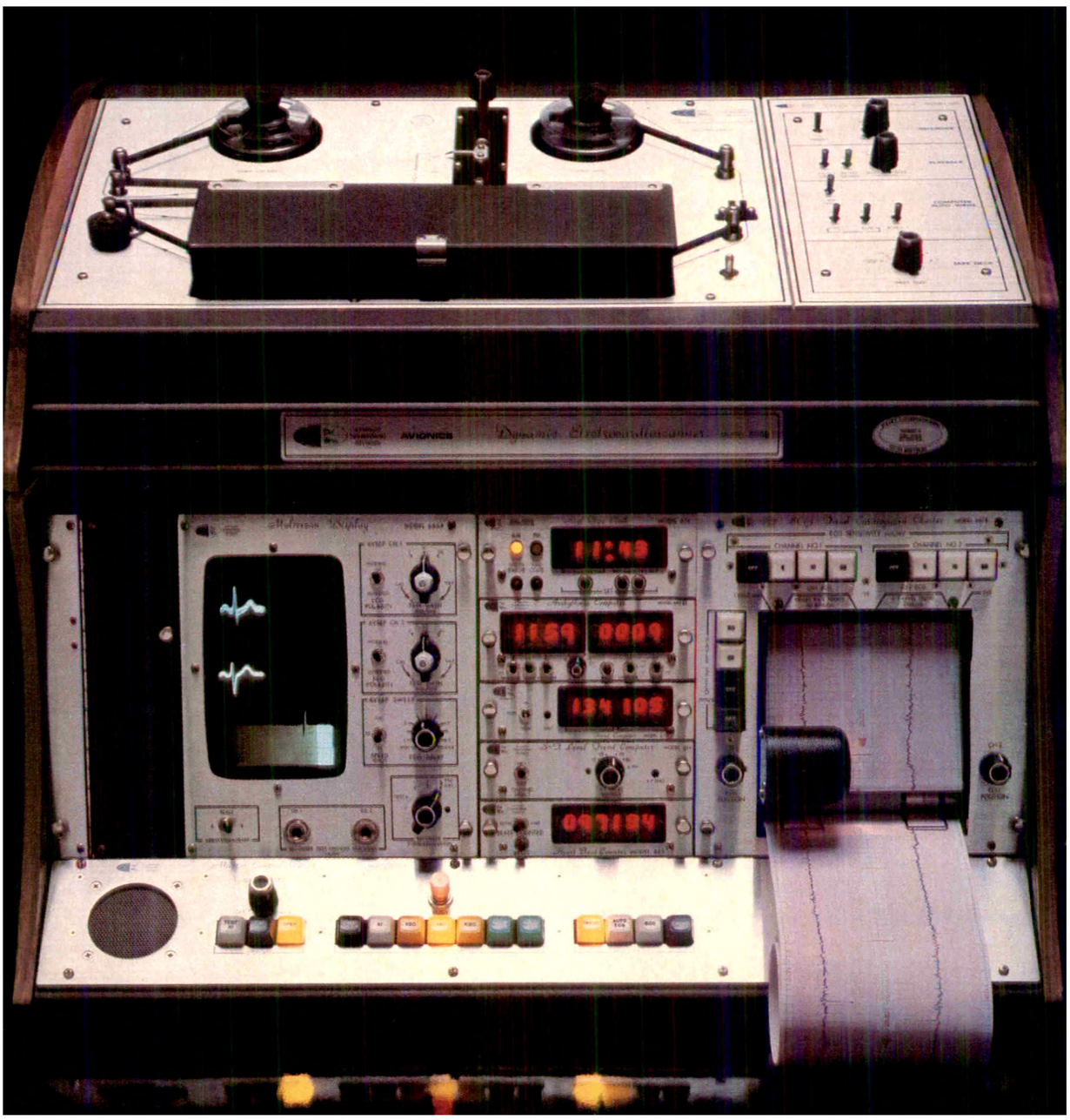


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Our other new Electrocardiocorder—the multichannel Model 448, is dedicated to recording and time-correlating implanted pacemaker pulses to the patient's ambulatory electrocardiogram. The 448 is the first Holter Monitor developed solely for the assessment of pacemaker function.

It's only natural Del Mar Avionics is first to offer you these diagnostic tools. We were first to develop practical ambulatory ECG recorders, first to utilize 2-channel recording, and first to offer 24 hours of continuous ECG information. After all, Holter Monitoring™ is our trademark.

But, this is only half the story.

The other half is our new Model 660B Electrocardioscanner®. Thread the tape, press a button and the 660B scans 24 hours of ECG and blood pressure information in 12 minutes, decoding the exact time of day directly from the tape. VE and SVE beats, heart rates, ST segment levels, and systolic/diastolic blood pressures are automatically categorized, quantified, and documented on a comprehensive trend chart.

With the trend chart completed, the 660B automatically rewinds and searches out abnormalities at 120-times real-time. Upon recognition, it precisely charts the abnormality, in real-time, with the exact time of occurrence.

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With all these innovations, putting the pressure on is our way of being first. At Del Mar Avionics, being the first has kept us first.





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A PIONEER IN CARDIOLOGY



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Inventor of the Stethoscope

Beginning his study of medicine at the age of 14, Dr. Laennec completed his education during the tumultuous days and aftermath of the French Revolution. Toward the end of his brief, brilliant career, in which he brought a new sense of order and discipline to the profession, Dr. Laennec brought about another revolution, no less dramatic for its absence of violence. His invention of the stethoscope and discovery of the principles of auscultation remain today landmarks in the development of knowledge of the human heart and chest.

Of Special Interest to Cardiologists

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During diuretic therapy for edema associated with congestive heart failure, conservation of vital potassium stores—so important in the patient receiving concomitant digitalis—is a basic action of the 'Dyrenium' component in 'Dyazide'.

Less critical, but important in fostering patient compliance with maintenance therapy, patients treated with 'Dyazide' seldom develop hypokalemia, often a factor in patients' decisions to abandon maintenance therapy because of muscle cramps, fatigue, and malaise.

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Serum K^+ and BUN should be checked periodically. (See warnings.)

'Dyazide' can cause hyperkalemia, though it is rare in patients with normal renal function. Serum K^+ and BUN should be checked periodically, particularly in elderly, diabetics, and those with suspected or confirmed renal insufficiency. Potassium supplements should not be used unless hypokalemia develops or dietary K^+ intake is markedly impaired. Not for initial therapy (see box warning).

See next page for brief summary of prescribing information.

SK&F CO.
Carolina, P.R.

SK&F Salutes
A Pioneer in Cardiology



RENÉ THÉOPHILE HYACINTHE LAENNEC
(1781-1826)

Inventor of the Stethoscope

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Potassium-Sparing Diuretic*

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Preexisting elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

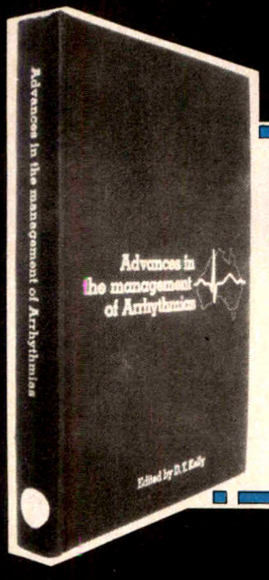
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July 20, 1978

...rold Hoosier 58, M Record #5542

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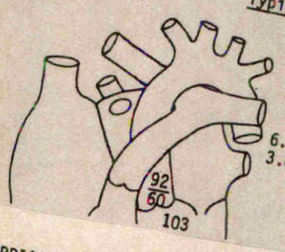
...for referring Mr. Hoosier to our laboratory to be
...as a candidate for coronary surgery. Mr. Hoosier was

CARDIAC DIAGNOSTIC AFFILIATES
University Community Hospital

CARDIAC CATHETERIZATION REPORT A - Page 2

Name: Harold Hoosier 58, M Record #5542
Date: 7/20/78 Ht: 155cm Wt: 80kg BSA: 1.78m2

Typical Hemodynamics



Sample Site	Pressure Data				
	Normal	Phasic	Mean	HR	Note
LV (mid)	140/12	87/1		72	1
LV OFT	140/12	103/14			
AO ASP	140/90	92/60	73	78	2

6.93L/min.
3.89L/min/m2

Note 1: Pre-angio with balloon off.
Note 2: Pullback, post-angio with balloon off.

CARDIAC DIAGNOSTIC AFFILIATES
University Community Hospital
56 Union Ave., Sudbury, Mass. 01776
Office: 617-443-9969
Hospital: 617-443-9886

CARDIAC CATHETERIZATION REPORT A

...ame: Harold Hoosier 58, M Record #5542
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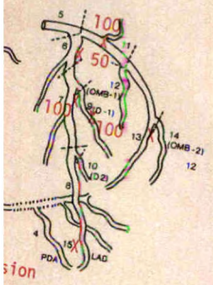
...ferring physician: John Woden, M.D.
...tending physician: Ward Halsom, M.D., Carol S. Perch, M.D.

...nical diagnosis: Pre-infarction angina / medical failure
...ication for study: Evaluate for coronary surgery

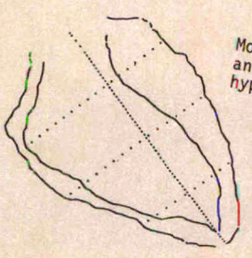
...edure: Hemodynamics: Left heart, right femoral approach
Angiography: LV, RAO view. Coronaries via Judkins.
Other: Performed during balloon counterpulsation
Complications: None.

...sion: 1. Good LV function, normal valves with mild anterolateral and infero-apical hypokinesis.
2. Severe 3-vessel coronary disease: 99% RCA occlusion, 50% proximal, 100% mid-LAD, 100% first diagonal, 100% proximal left circumflex.
3. Retrograde filling of LAD from proximal RCA and posterior descending, plus collaterals to the circumflex show good distal vessels.

...ation: Coronary artery bypass graft surgery--immediate standby basis.



...sion
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Moderate anterolateral hypokinesis

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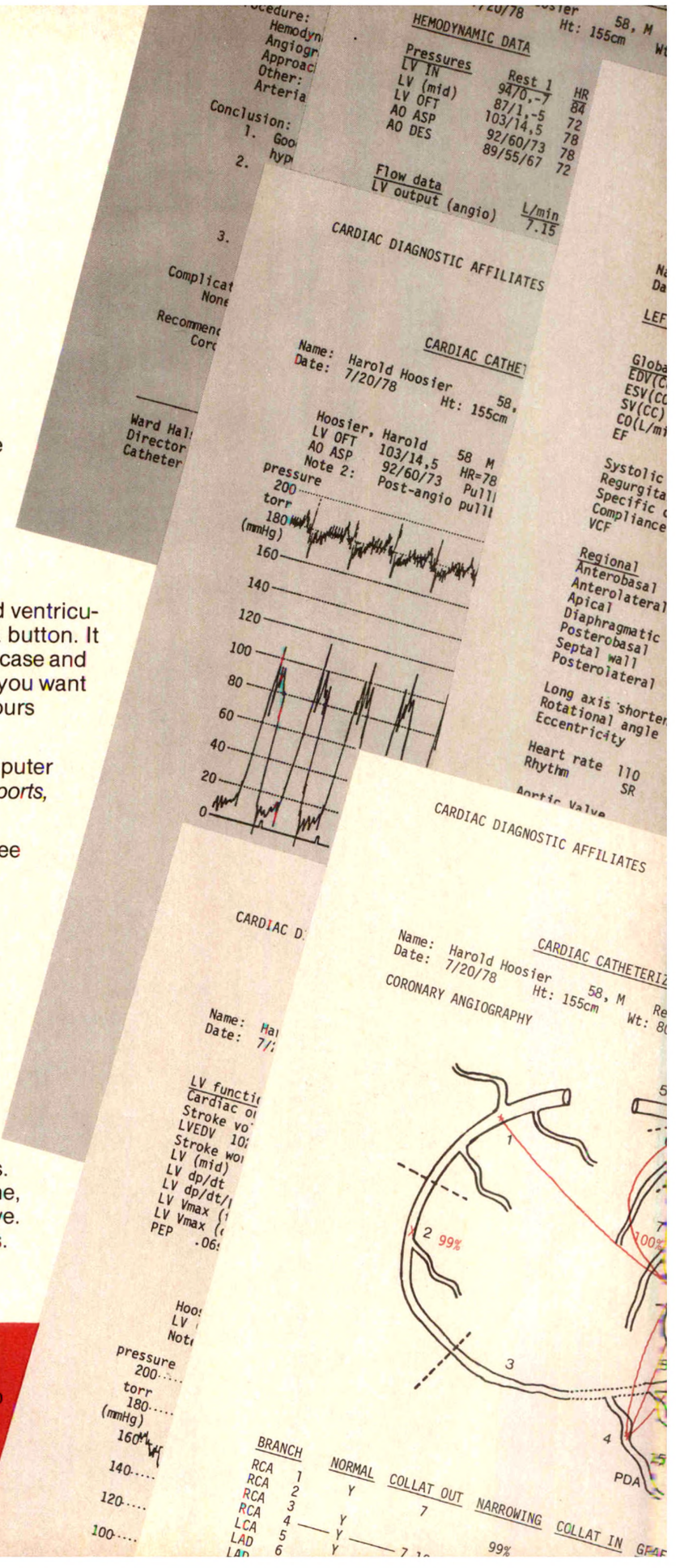
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IN THE ANXIOUS POST-MI PATIENT

THESE PARAMETERS MAY BE IMPROVING...



The patient's ECG shows an improved picture with virtually no signs of the S-T segment shift associated with myocardial injury. Both the erythrocyte sedimentation rate and the SGOT are now within normal limits. Blood pressure readings are on the low side and the patient's pulse rate is down to 80 beats per minute. The atrial gallop sound can no longer be heard.

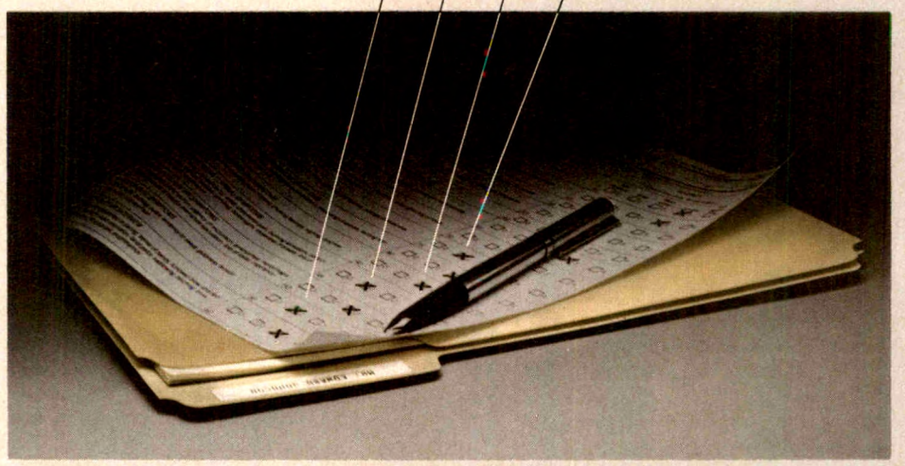
BUT THESE MAY NOT.

You've assured the patient, time and again, that he's making excellent progress, that all signs point to a marked improvement in his condition. He *seems* to understand... and yet, his excessive anxiety and psychic tension continue to pose problems.

For patients like this, adjunctive Valium (diazepam) can be particularly useful. Valium works promptly: patients often feel distinctly calmer in hours, usually report significant symptomatic relief within days. And once calmer and in better control of their emotions, they tend to be more optimistic as well and to enter more willingly into rehabilitative programs.

Valium can also alleviate the anxiety-linked insomnia so often seen in post-MI patients. In most cases, adding an *h.s.* dose of Valium to the usual *t.i.d.* schedule helps relieve "nighttime apprehensions" and encourages sleep. And Valium is used with most classes of primary medications, including cardiac glycosides, anticoagulants, diuretics and vasodilators.

An especially important advantage: Valium (diazepam) is usually well tolerated. Though drowsiness, ataxia and fatigue are encountered with some patients, these and more serious side effects are rarely a problem. Patients who will be taking Valium during their first weeks at home should be cautioned against the simultaneous drinking of alcohol. Periodic reassessment of the patient's need for psychotropic medication is also recommended.



VALIUM® (IV)
diazepam/Roche
2-mg, 5-mg, 10-mg scored tablets

TO REDUCE EXCESSIVE ANXIETY TO MORE MANAGEABLE LEVELS

Before prescribing, please see following page for a summary of product information.

ROCHE

Valium® (diazepam/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps; vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

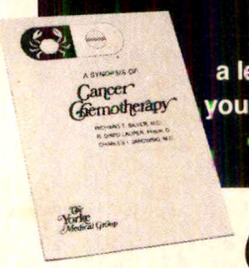
Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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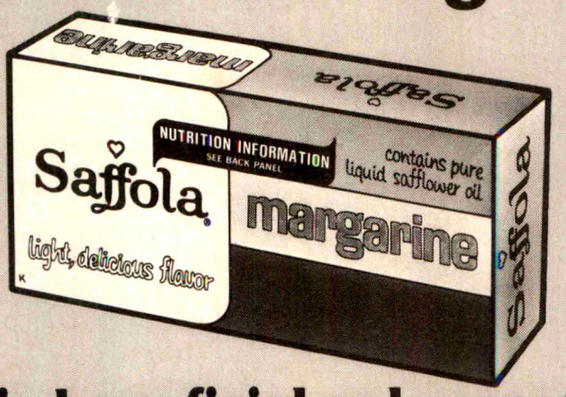
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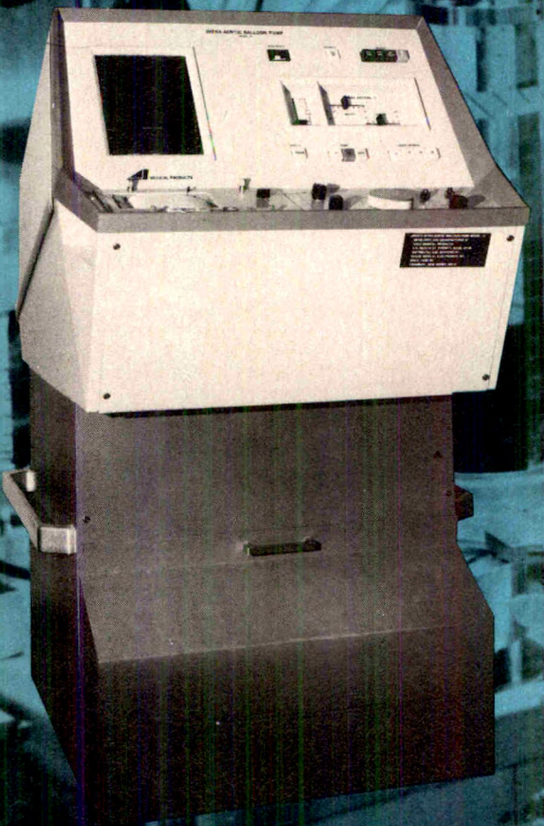
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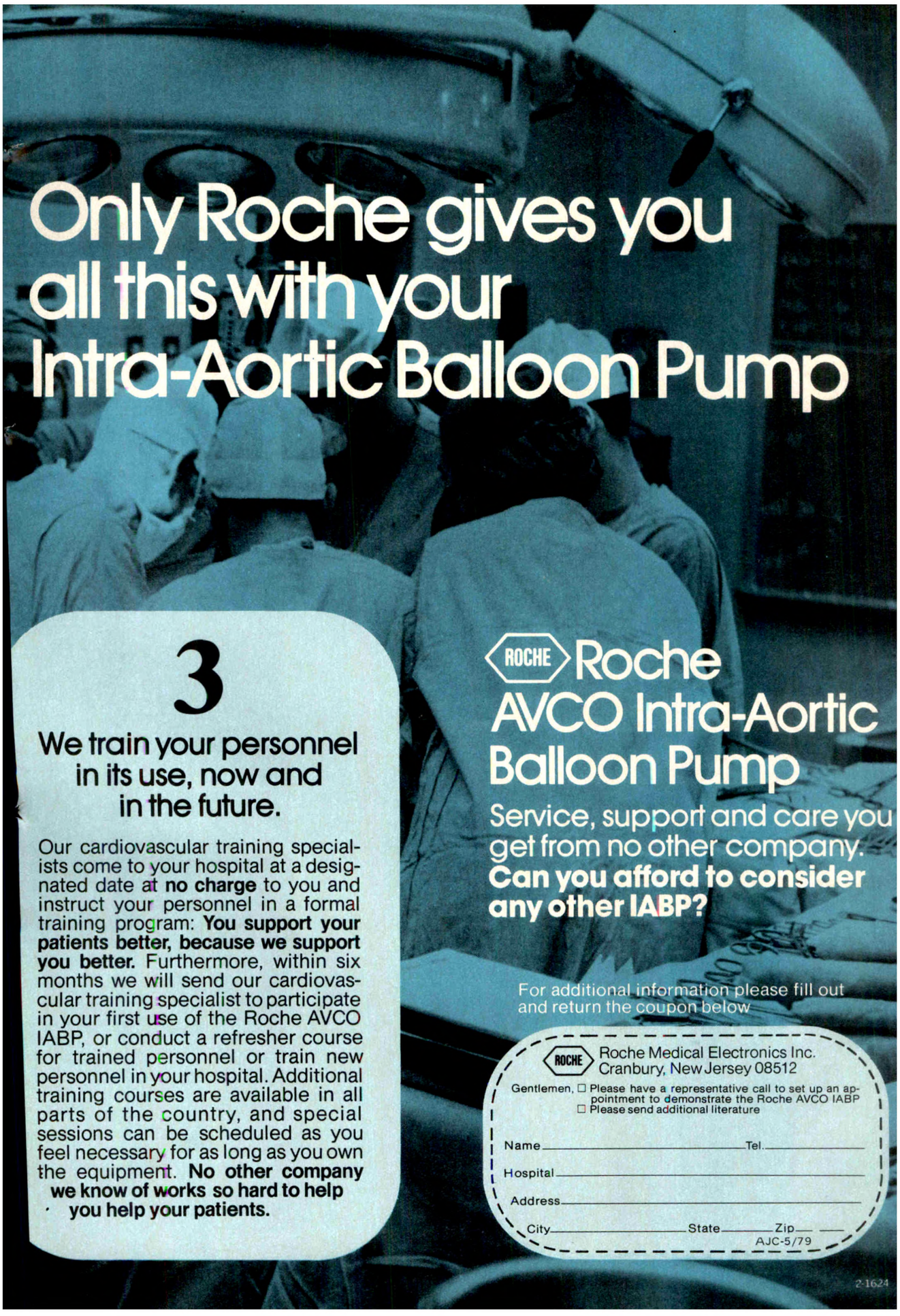
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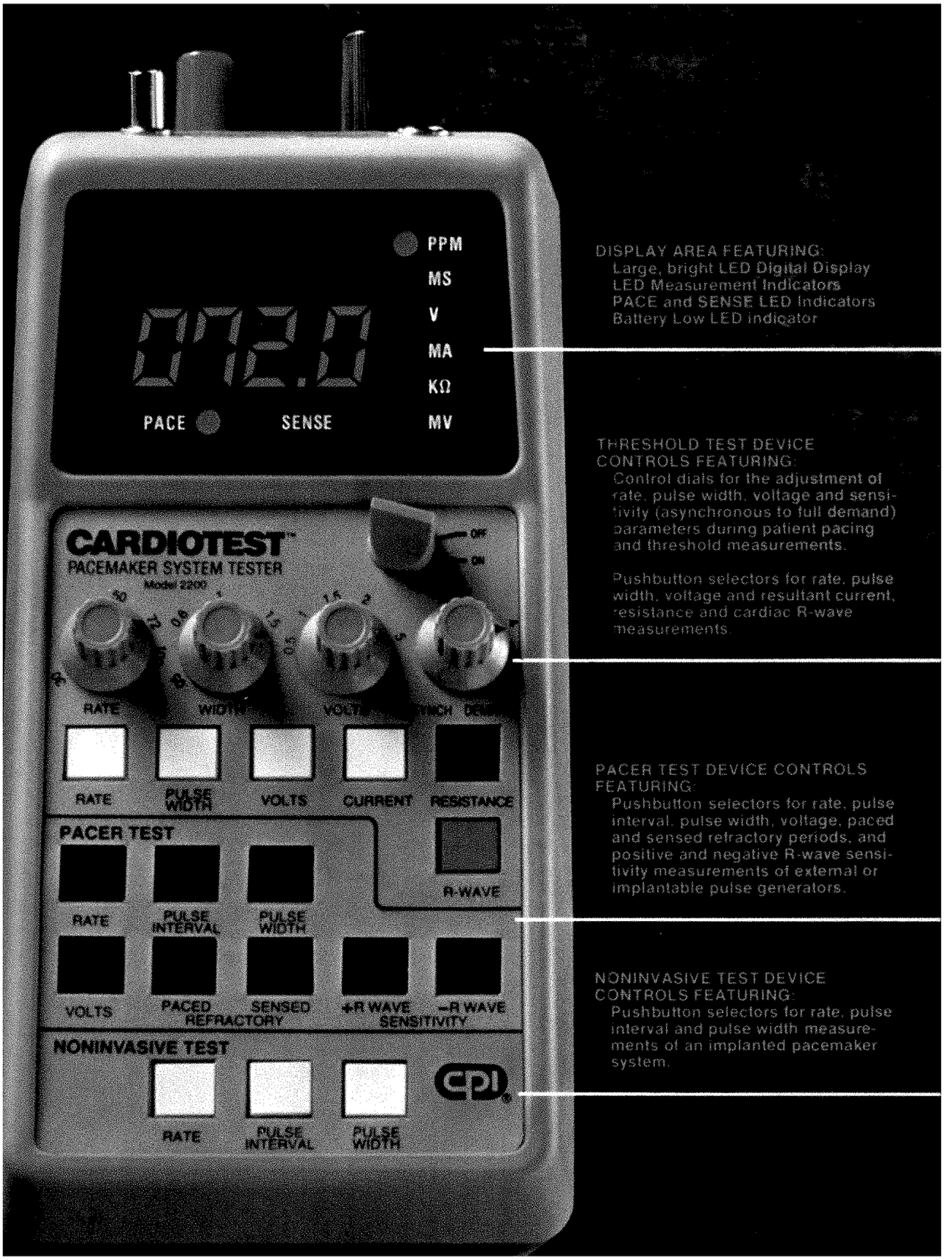
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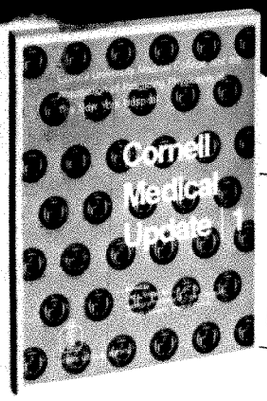
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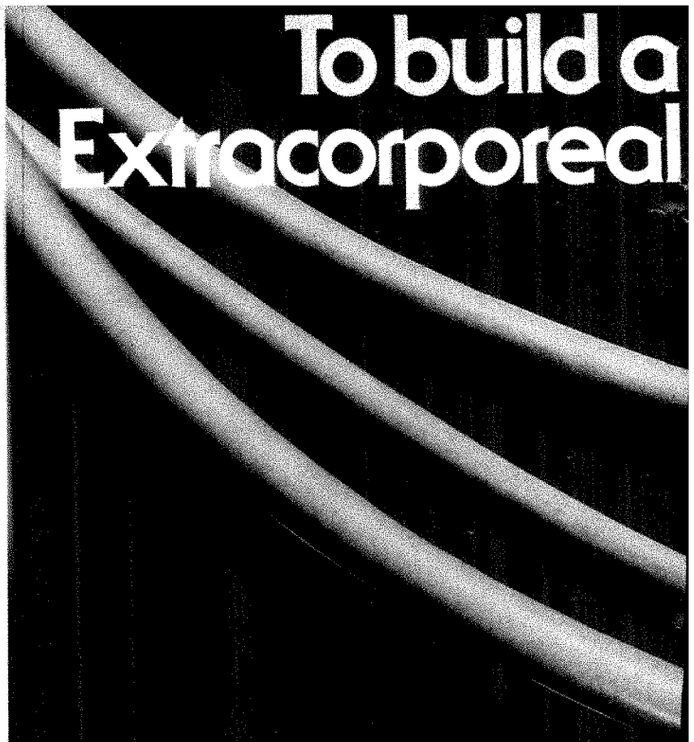
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Indications: For sampling blood for oxygen levels and measuring pressures in the right heart, including central venous, right ventricular, pulmonary artery, and pulmonary artery wedge pressure. Also indicated in anatomical cardiac defect cases to sample blood and measure pressures in any chamber that can be entered from the right heart. **Warning:** Pulmonary artery perforation, thrombosis, segmental pulmonary infarction, transient obstruction of the pulmonary outflow by the inflated balloon, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of the catheter have been reported as complications of the use of balloon cathete Balloon rupture with possible latex embolus is a potential complication in the use of balloon catheters. **Precaution:** In pressure monitoring at bedside when catheter has been introduced in an antecubital vein, patient's arm should be immobilized to reduce the possibility of catheter advancement d to arm motion.

BERMAN ANGIOGRAPHIC CATHETER

Indications: For use in right-heart catheterization for cardiac angiography, pulmonary angiography, and measurement of right-heart and pulmonary artery pressures. It can be used to inject radiopaque media and measure pressures in any chambers and vessels that can be entered from the right heart. **Warnings:** Angiograms should be done with balloon inflated to minimize myocardial staining. When injecting radiopaque media, do not exceed stated maximum flow rate and pressure. Transient obstruction of the pulmonary outflow tract, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of catheters are reported complicati of the use of balloon catheters. Balloon rupture with possible latex embolu is a potential complication in the use of balloon catheters. **Precaution:** Mar ulate catheter carefully and gently to avoid kinking or knotting.

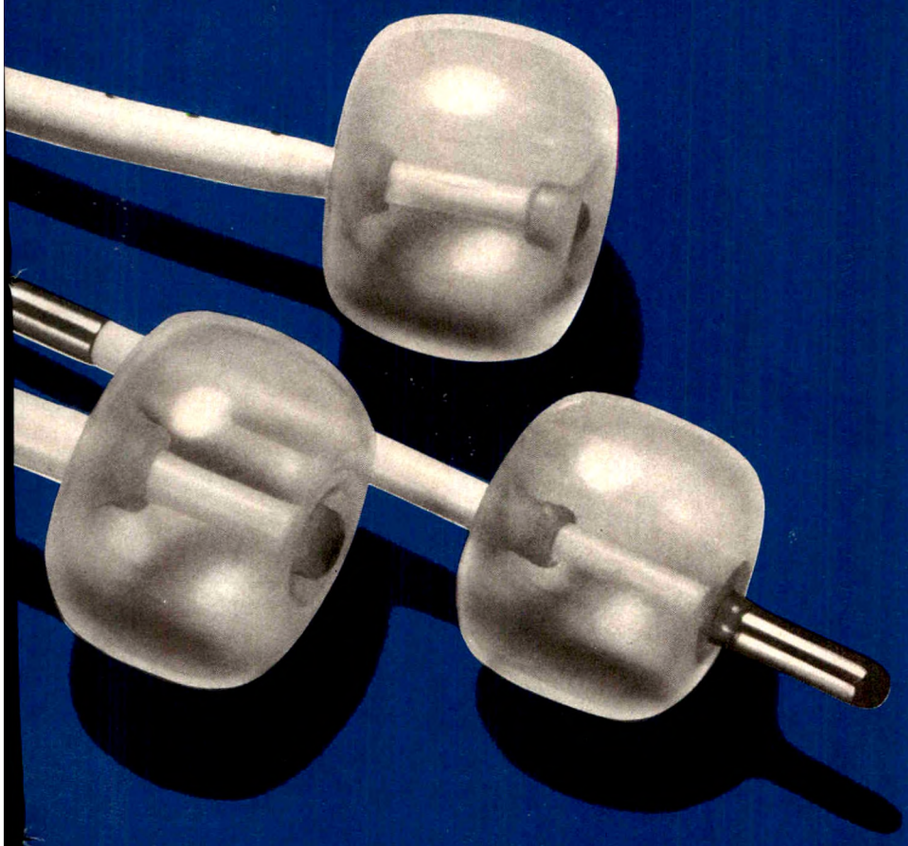
BIPOLAR TEMPORARY PACING W/STYLET AND BALLOON TEMPORARY PACING CATHETERS

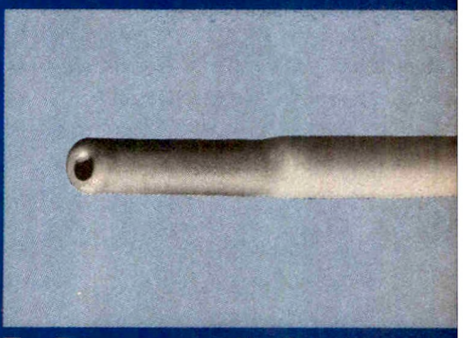
Indications: For temporary transvenous cardiac pacing when impulse form tion or conduction is impaired. **Warnings:** Myocardial perforation, fibrillatic and arrhythmia, pulmonary embolism, thrombus formation, and infection a general complications of transvenous pacing. Balloon rupture with possib latex embolus, vessel perforation, and intimal disruption are potential com plications of use of balloon temporary pacing catheters. With the transbrachial approach, malpositioning and perforation occur more frequently due to arm movement. Pneumothorax, air embolism, and puncture of the subclavian artery have been reported with the subclavian approach. **Precautions:** Avoid kinking or bending catheter to prevent damage to interna wires or occlusion of inflation lumen (in balloon pacing catheter). Maintain insertion site with regular meticulous redressing performed with aseptic technique. Remove stylet from Bipolar Pacing Catheter after it is in positi because leaving stylet *in situ* increases the potential for perforation.

FOR BALLOON CATHETER USE, IN GENERAL

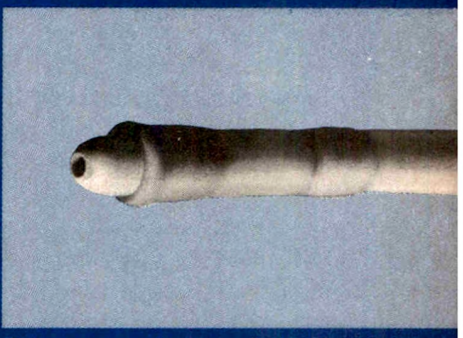
General Warnings: Carbon dioxide must be used to inflate balloon if there a possibility that balloon rupture would result in air embolism in the left he or systemic circulation. Do not inflate balloon beyond stated maximum inflation capacity. Exercise care when passing catheters in patients with l bundle-branch block because right bundle-branch block induced by traumatic catheter passage could result in complete heart block and asystole. **General Precautions:** Do not use liquids as balloon-inflation media. Pass catheter with continuous cardiographic monitoring and fluoroscopic guidance, and confirm final tip position by X-ray. Deflate balloon prior to withdrawing catheter to avoid possible valve damage. Use aseptic technique throughout procedure. All catheters are for single use only. Do not reste or reuse. Federal law (U.S.A.) restricts these devices to sale by or on the order of a physician. **Contraindication:** Not for use except as indicated

better cardiac catheter, starts with a built-in tip.





The Extracorporeal built-in tip, balloon deflated.



Other manufacturer's built-on tip, balloon deflated.

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- **More sizes available.** Especially in Berman angiographic and wedge pressure models. And we can supply custom catheters, too.
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- **Our new brochure has all the facts.** Just let us know where you are and we'll send you one. Call your Extracorporeal representative, or write or call us toll free: 800-523-1740.

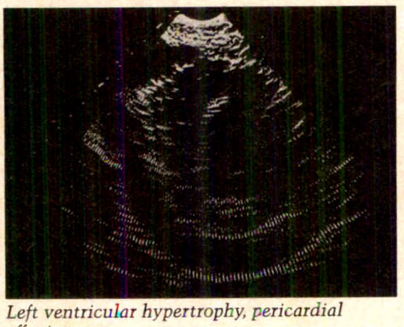
*With one small exception—the Extracorporeal 4F size uses a 4-1/2 size introducer.

extracorporeal

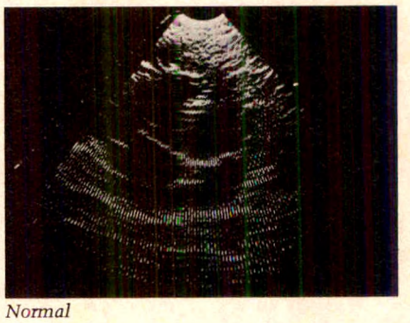
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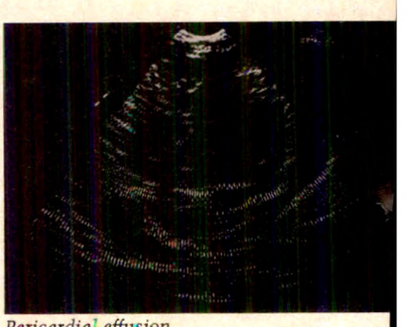
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Left ventricular hypertrophy, pericardial effusion.



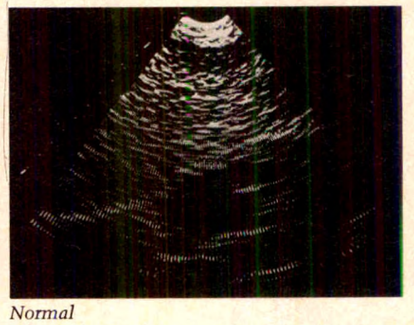
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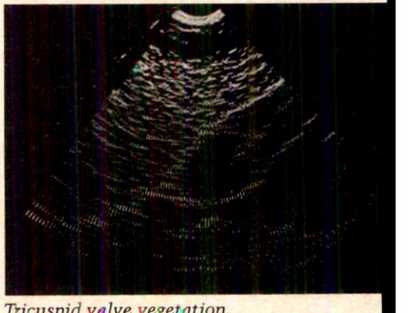
Pericardial effusion.



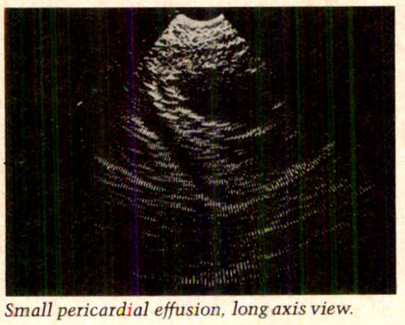
Inferior Vena Cava entering right atrium.



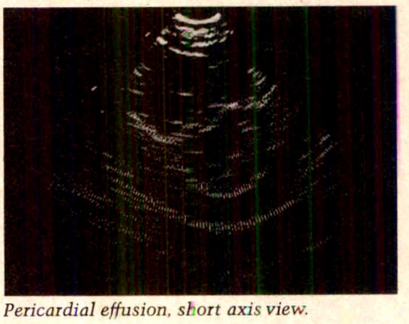
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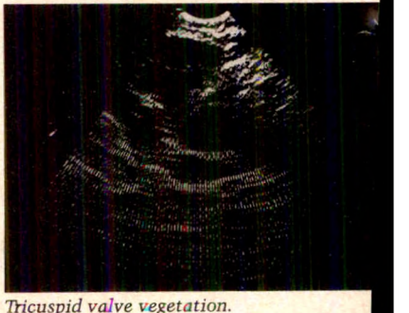
Tricuspid valve vegetation.



Small pericardial effusion, long axis view.



Pericardial effusion, short axis view.



Tricuspid valve vegetation.

Our patented method of Dynamic Image Reconstruction significantly improves image quality, data storage and the ease of making a diagnosis.

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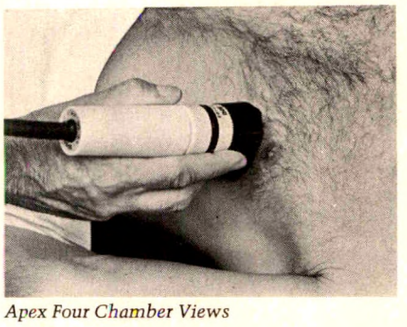
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Images recorded with the Dynamic Image Reconstruction

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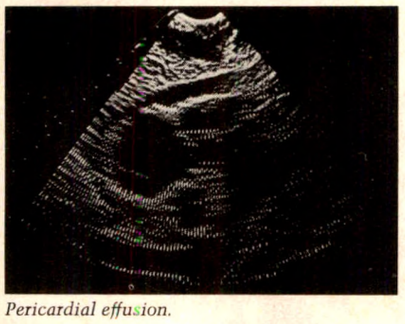


Mitral valve prolapse.

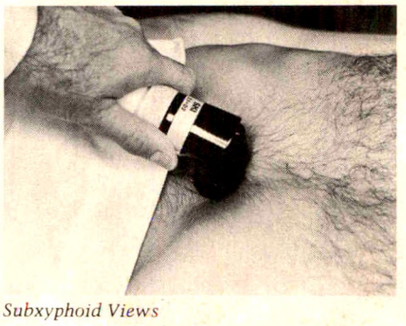


Apex Four Chamber Views

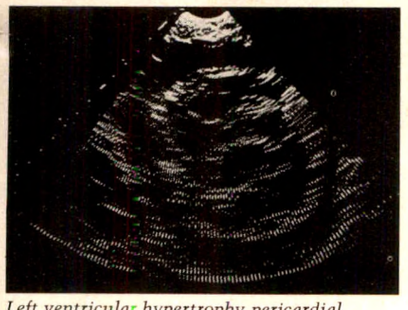
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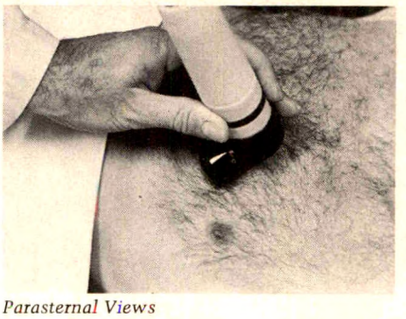
Pericardial effusion.



Subxyphoid Views



Left ventricular hypertrophy pericardial effusion, short axis.



Parasternal Views



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For ventricular arrhythmias.
For atrial arrhythmias.
For smooth, trouble-free conversion.
For steady maintenance.



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TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

Purdue Frederick

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JUNE 1979

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Mechanisms of Coronary Arterial Spasm

Myocardial Infarction in Hypertrophic Cardiomyopathy

Seminar on Thrombosis

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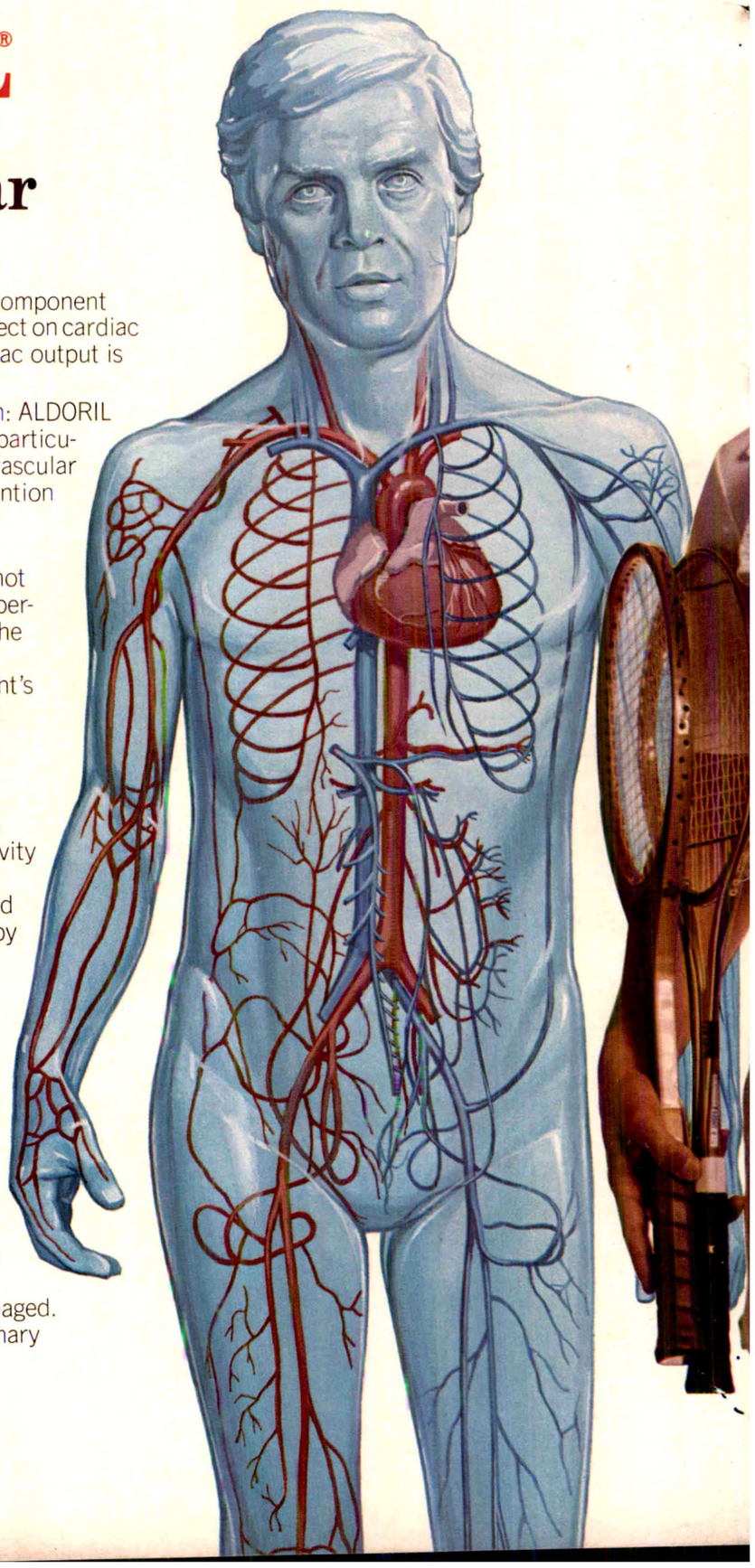
ALDORIL®
from the cardiovascular viewpoint

- ☐ A favorable cardiac profile: neither component of ALDORIL usually has any direct effect on cardiac function—in long-term therapy cardiac output is usually maintained.
- ☐ Control of sodium and fluid retention: ALDORIL often helps control fluid imbalance, particularly in those cases of hypertensive vascular disease where sodium and water retention is a problem.

As a fixed combination, ALDORIL is not indicated for initial therapy since hypertension requires therapy titrated to the individual patient. If an available strength of ALDORIL meets the patient's titrated needs, the combination drug may be more convenient in patient management. Therapy should be reevaluated as necessary.

ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.



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active hypertensives points of view



ALDORIL®
from the practical viewpoint

- ☐ Highly effective complementary agents: HydroDIURIL® (Hydrochlorothiazide, MSD), and ALDOMET® (Methyldopa, MSD), two well-accepted antihypertensives which usually maintain blood pressure control throughout the day.
- ☐ Greater dosage convenience (with a single tablet): a b.i.d. regimen is possible for many patients.
- ☐ Effect on daily activities usually minimal: there is less frequent symptomatic postural hypotension with ALDORIL than with many other antihypertensive agents. Exercise hypotension and diurnal blood pressure variations rarely occur.

ALDORIL®

containing methyldopa and hydrochlorothiazide

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containing 500 mg ALDOMET® (Methyldopa, MSD) and 50 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
ALDORIL® D30
containing 500 mg ALDOMET® (Methyldopa, MSD) and 30 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
ALDORIL®-25 containing 250 mg ALDOMET® (Methyldopa, MSD) and 25 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS
ALDORIL®-15 containing 250 mg ALDOMET® (Methyldopa, MSD) and 15 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

For a brief summary of prescribing information, please see following page.

MSD
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Antihypertensive TABLETS
ALDORIL® D50
methyldopa 500 mg and hydrochlorothiazide 50 mg

Antihypertensive TABLETS
ALDORIL® D30
methyldopa 500 mg and hydrochlorothiazide 30 mg

Antihypertensive TABLETS
ALDORIL®-25
methyldopa 250 mg and hydrochlorothiazide 25 mg

Antihypertensive TABLETS
ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without mild edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL® D30, containing 500 mg methyldopa and 30 mg hydrochlorothiazide, bottles of 100; Tablets ALDORIL® D50, containing 500 mg methyldopa and 50 mg hydrochlorothiazide, bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486. 8AR09(023)

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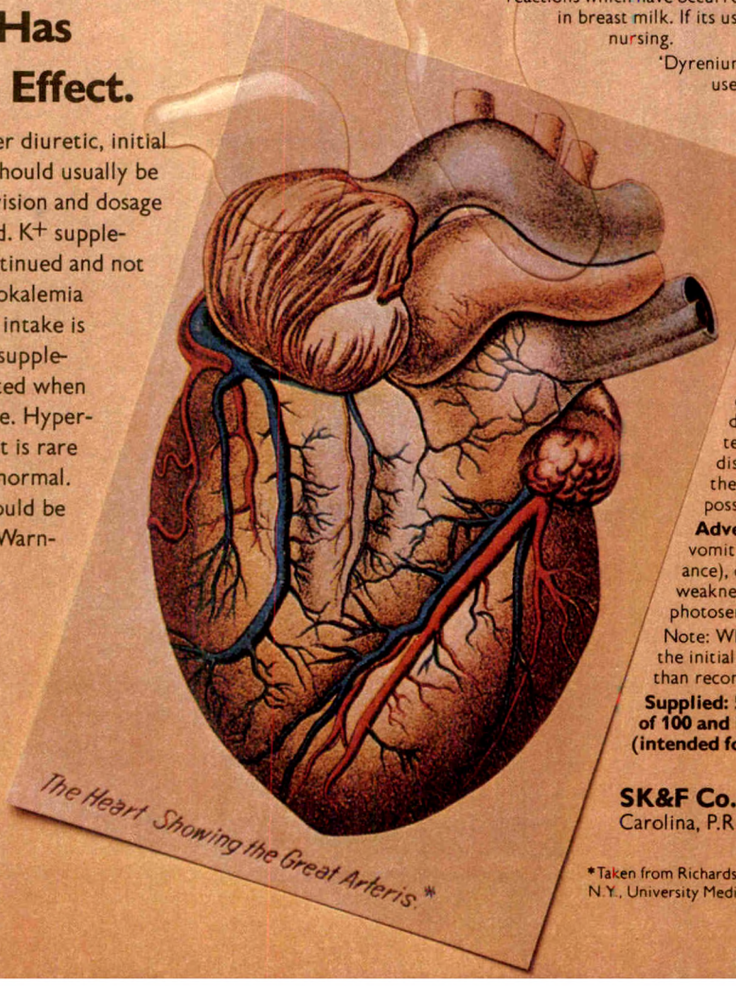
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In a study of 30 cardiac patients (10 as controls, 20 receiving furosemide), 'Dyrenium' (200 mg./day) was added to 10 of the treated patients. After at least 10 days on the combined regimen, mean plasma potassium was significantly increased from pre-'Dyrenium' levels of 3.85 mEq./l. (±.12) to 4.54 mEq./l. (±.12). Any K+ supplements were discontinued.[1]

'Dyrenium' Has an Additive Effect.

When used with another diuretic, initial dosage of both agents should usually be reduced; careful supervision and dosage adjustment are required. K+ supplements should be discontinued and not reinstituted unless hypokalemia develops or dietary K+ intake is markedly reduced. K+ supplements are contraindicated when 'Dyrenium' is used alone. Hyperkalemia can occur, but it is rare when renal function is normal. Serum K+ and BUN should be checked regularly (see Warnings below).

1. Donaldson, E.K., et al.: *Brit. M.J.* 1:1254-5 (May 22) 1976.



*The Heart Showing the Great Arteris.**

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing.

'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Triamterene is a weak folic acid antagonist. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 50 and 100 mg. capsules, in bottles of 100 and in Single Unit Packages of 100 (intended for institutional use only).

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Carolina, P.R.

*Taken from Richardson, J.G.: Medicology. N.Y., University Medical Society. 1906.

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Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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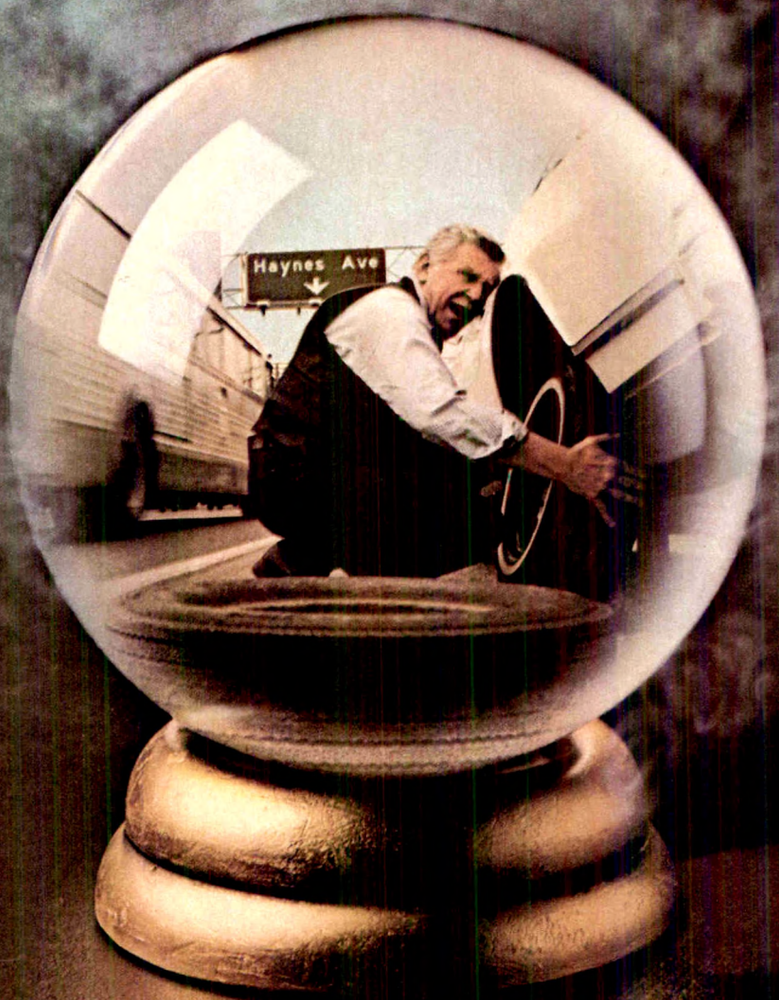
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SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing, transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE® (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

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CLINICAL STUDIES

1073 Altered Adrenergic Activity in Coronary Arterial Spasm: Insight Into Mechanism Based on Study of Coronary Hemodynamics and the Electrocardiogram

DONALD R. RICCI, ARTHUR E. ORLICK, PAUL R. CIPRIANO, DIANA F. GUTHANER and DONALD C. HARRISON

The data in this prospective study of eight patients with clinical features of Prinzmetal's variant angina pectoris suggest that alterations in the sympathetic stellate ganglion activity and transient alpha adrenergic receptor stimulation can presage the development of coronary arterial spasm in some patients with this condition. During spontaneous or provoked attacks of angina due to coronary spasm, phentolamine relieved chest pain, reduced coronary vascular resistance, reversed coronary spasm and returned the electrocardiographic pattern to the control state. In four patients the administration of the long-acting oral alpha blocking agent phenoxybenzamine (20 to 80 mg/day) caused the disappearance of symptoms during a 3 to 12 month follow-up period.

1080 Variant Angina Pectoris: Investigation of Indexes of Sympathetic Nervous System Function

DAVID ROBERTSON, ROSE M. ROBERTSON, ALAN S. NIES, JOHN A. OATES and GOTTLEIB C. FRIESINGER

Although the underlying mechanism remains unknown, coronary arterial vasospasm has been demonstrated in variant angina with and without myocardial infarction. These investigations of autonomic function in three patients do not support the concept of a generalized increase in sympathetic outflow in this condition. Observations in 1,045 spontaneous episodes of S-T segment elevation in the three patients over a total of 72 days of continuous electrocardiographic monitoring indicate that the severity of vasospastic angina fluctuates markedly and spontaneously. Eighty-nine percent of episodes were asymptomatic. Nitroglycerin regularly relieved angina or S-T elevation, or both. Controlled trials of propranolol showed no significant beneficial effect. The variable course of variant angina, with spontaneous and long-lasting remissions, necessitates cautious interpretation of clinical therapeutic trials.

1086 Hypertrophic Cardiomyopathy and Transmural Myocardial Infarction Without Significant Atherosclerosis of the Extramural Coronary Arteries

BARRY J. MARON, STEPHEN E. EPSTEIN and WILLIAM C. ROBERTS

Transmural myocardial infarction in the absence of significant coronary atherosclerosis occurred in 15 percent of 82 patients over the age of 10 years who died from hypertrophic cardiomyopathy. These data indicate that transmural infarction is likely to contribute to the clinical deterioration of some patients with hypertrophic cardiomyopathy, leading to ventricular dilatation, progressive fatal cardiac failure and supraventricular arrhythmias. None of the seven patients had typical angina pectoris; one had a clinical episode consistent with acute myocardial infarction. Mural thrombi in the left ventricle occurred in four of the seven patients. Although several possibilities are considered, the etiology of transmural myocardial infarction in these patients remains unclear.

Continued on page A15

The heart of the matter is the kidney



BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. Using mothers. Thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolyte. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (severe liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patie

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may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary, with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) and 25 mg. (peach) in bottles of 100 and 1000, unit-dose blister packs, boxes of 100 (10 x 10 strips). Also, 100 mg. and 50 mg. in PAKs of 28 tablets, boxes of 6.

References: 1. Finnerty, F.A. Jr.: Managing Mild Hypertension: A low-dose approach. Scientific Exhibit presented at Amer. Coll. Cardiol. 28th Annual Scientific Session, Miami Beach, Fla., Mar. 11-15, 1979. **2.** Materson, B.J. et al.: Dose response to chlorthalidone in patients with mild hypertension. Clin. Pharmacol. Ther. 24:192, 1978. **3.** Data on file, USV Laboratories Inc.

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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.
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1103 Occlusive Disease Confined to the Right Coronary Artery: Clinical Features, Surgical Treatment and Long-Term Follow-Up in 124 Patients

MICHELE A. CODINI, PHILIP W. HASSAN, ROBERT G. HAUSER, MARSHALL D. GOLDIN and JOSEPH V. MESSER

Although the excellent prognosis in patients with single vessel disease, particularly those with isolated right coronary arterial narrowing usually provides a strong argument against surgery, coronary bypass grafting was performed for relief of symptoms in 124 patients with isolated right coronary artery disease. The operative mortality was 1.6 percent and the 5 year mortality rate 4.0 percent; the incidence of perioperative myocardial infarction was 5 percent. Eight patients required reoperation because of recurrence of symptoms, occlusion of the graft or progression of occlusive disease of other major coronary arteries, or both. Bypass surgery for isolated right coronary artery disease had a low mortality rate and resulted in excellent long-term symptomatic improvement. Such surgery appears justified in patients with severe isolated right coronary disease who are highly symptomatic or who have malignant tachyarrhythmias, or both.

1109 Revascularization of the Right Coronary Artery

HILLEL LAKS, GEORGE C. KAISER, J. GERARD MUDD, JOHN HALSTEAD, GLENN PENNINGTON, DENNIS TYRAS, JOHN CODD and HENDRICK B. BARNER

This comparison of the proximal arterial lesions in 170 patients with grafts to the right coronary artery and in 71 patients with an ungrafted right coronary artery showed significant progression of stenosis in 83 percent and 26 percent, respectively, among vessels with initially less than 50 percent narrowing; progression to total occlusion occurred in 28 percent and 3 percent, respectively. Progression to total occlusion was more frequently associated with a patent than with an occluded graft and more common in arteries with greater than 70 percent narrowing. These investigators currently perform coronary bypass grafting in all patients whose right coronary artery has a lesion of 50 percent or greater. The high rate of progression of proximal disease and occlusion, once the vessel is bypassed, makes the vessel totally dependent on vein graft patency.

1114 Poststress Redistribution of Thallium-201 in Patients With Coronary Artery Disease, With and Without Prior Myocardial Infarction

MARIO S. VERANI, SATISH JHINGRAN, MOHAMMED ATTAR, ASSAD RIZK, MIGUEL A. QUINONES and RICHARD R. MILLER

Thallium-201 myocardial perfusion scintigraphy performed immediately after exercise and 4 to 6 hours after exercise in 46 subjects with coronary artery disease and in 12 normal control subjects showed a considerable overlap in redistribution scintigrams in those with coronary artery disease with and without prior infarction. There was a high incidence rate of rate-related transient stress-induced hypoperfusion in both infarcted and noninfarcted myocardium. In addition, resting scintigrams may be needed in many patients because the delayed post exercise redistribution imaging may not discriminate between myocardial scar and ischemia. An additional important finding was that thallium-201 imaging identified transient myocardial hypoperfusion in sites other than the site of infarction in 59 percent of the patients with prior infarction. This study also confirms the decreased sensitivity of the stress electrocardiogram in identifying ischemia and indicates that postexercise immediate and delayed perfusion images are superior in detecting ischemia in the presence of prior myocardial necrosis.

1123 Infection of Glutaraldehyde-Preserved Porcine Valve Heterografts

VICTOR J. FERRANS, STEVEN W. BOYCE, MARGARET E. BILLINGHAM, THOMAS L. SPRAY and WILLIAM C. ROBERTS

Gross, histologic and ultrastructural changes associated with bacterial infection in four glutaraldehyde-preserved porcine valve heterografts and published reports of 43 other patients with similar infection indicate that the infection in these valves (1) develops in the fibrin layer covering the cusps, (2) can involve the collagen in the leaflets, and (3) is uncommonly (3 patients) associated with valve ring abscesses. Such infection has a high mortality rate, although it is not frequently associated with valve ring abscesses. The single factor most frequently identified as predisposing to infection of porcine valve heterografts was opiate addiction (five patients). Valve dys-

Continued on page A17

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function occurred in 14 of the infected heterografts. Porcine valve heterografts, probably because of the glutaraldehyde treatment, are less easily destroyed by infection than are native valves, homografts or fascia lata valves.

EXPERIMENTAL STUDIES

1137 Effect of Diltiazem, a Calcium Antagonist, on Myocardial Ischemia

RONALD WEISHAAR, KOUICHI ASHIKAWA and RICHARD J. BING

In dogs with experimentally produced myocardial ischemia the administration of diltiazem hydrochloride, a potent calcium antagonist and a coronary vasodilator, halved the decrease in adenosine-5-triphosphate in the ischemic area, reduced inhibition of anaerobic glycolysis, lowered the tissue levels of lactic acid and free fatty acids, improved the contractility of glycerinated heart muscle fibers, but failed to influence mitochondrial function. These results demonstrate that diltiazem can minimize the consequences of acute myocardial ischemia, but its beneficial effects do not extend to all aspects of disturbed myocardial metabolism.

1144 Reduction of Intimal Thickening in Canine Coronary Bypass Vein Grafts With Dipyridamole and Aspirin

MICHAEL P. METKE, J. T. LIE, VALENTIN FUSTER, MIGUEL JOSA and MICHAEL P. KAYE

Angiographic and postmortem data indicate that the degree of early intimal thickening that persists 2 to 6 months postoperatively in canine coronary bypass vein grafts may be significantly reduced by the platelet inhibitor combination of dipyridamole plus aspirin. Significant asymmetric intimal thickening was present in seven of nine untreated animals. For the treated group only two of the nine had intimal thickening similar in severity to that of the untreated group; the remaining series had only minimal thickening. In view of these results, the design of clinical trials to test the protective effects of this drug combination is now fully justified in patients undergoing aortocoronary bypass surgery.

1149 Canine Electrophysiology of Encainide, a New Antiarrhythmic Drug

MAGDI SAMI, JAY W. MASON, GEORGE OH and DONALD C. HARRISON

Encainide, a new benzanillide derivative, prolongs His-Purkinje system conduction without significantly affecting conduction or refractoriness of other parts of the cardiac conduction system in animals. It prolonged the H-V interval and QRS duration at doses of 0.9 mg/kg and greater without significant changes in sinus cycle length, blood pressure or the A-H or Q-Tc interval. Presumably encainide prevents or abolishes reentrant ventricular arrhythmias by its action of prolonging His-Purkinje system conduction. It should be safe to give with beta adrenergic blocking agents or calcium antagonists but not with quinidine-like drugs, which also prolong the H-V interval and QRS duration.

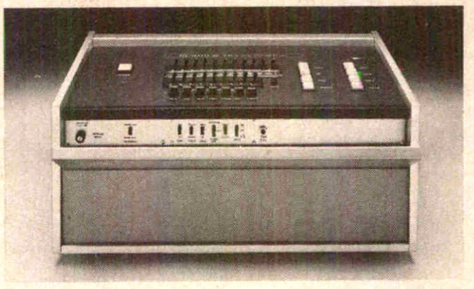
1155 Effects of Thioridazine (Mellaril) on Ventricular Electrophysiologic Properties

MYUNG S. YOON, JAOK HAN, GEORGE H. DERSHAM and SUSAN A. JONES

Electrophysiologic studies with therapeutic and toxic doses of thioridazine (Mellaril) in 12 anesthesized dogs show its antiarrhythmic and arrhythmogenic effects are dose-dependent. These results confirm the quinidine-like action of thioridazine when it is administered in a therapeutic dose (10 mg/kg), but the drug increased ventricular vulnerability to arrhythmias when given in a toxic dose (50 mg/kg). Diastolic threshold, effective refractory period and conduction time are significantly increased and idioventricular automaticity is suppressed by a therapeutic dose of thioridazine. Toxic doses augment these changes. These results confirm the possible life-threatening cardiac complications of thioridazine and suggest caution in dosage and frequent monitoring of electrocardiograms and blood pressure in patients receiving large doses of phenothiazine derivatives.

Continued on page A19

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CONTENTS

METHODS

1159 Multiple Gated Cardiac Blood Pool Imaging for Left Ventricular Ejection Fraction: Validation of the Technique and Assessment of Variability

FRANS J. TH. WACKERS, HARVEY J. BERGER, DAVID E. JOHNSTONE, LEE GOLDMAN, LAWRENCE A. REDUTO, RENE A. LANGOU, ALEXANDER GOTTSCHALK, BARRY L. ZARET. With the technical assistance of LENNY QUARTARARO and LINDA PYTLIK

In 83 patients ejection fraction by gated studies correlated well with data from first pass radionuclide angiocardiography and from contrast angiography. However, differential variability was noted and should be considered in interpreting sequential changes in left ventricular ejection fraction. Before being attributed to nonrandom physiologic alterations, the absolute change in ejection fraction should be 10 percent or more in patients with a normal heart and more than 5 percent in patients with an abnormal heart. Smaller changes may be significant in immobilized patients. Consistent trends of smaller magnitude in large groups of patients also may prove significant.

1167 Clinical Evaluation of Automated Processing of Electrocardiograms by the Veterans Administration Program (AVA 3.4)

CHRISTIAN R. BROHET and HAROLD G. RICHMAN

This clinical evaluation of automated processing of 1,000 unselected electrocardiograms by two reviewer groups, one familiar with and the other unfamiliar with the computer program, indicates that the diagnostic performance of the Veterans Administration program is clinically satisfactory but that the degree of physician education required to achieve acceptance of the program is greater than that required for most programs utilizing conventional criteria. The flexibility of interpretation by statistical decision offers the potential for better diagnostic accuracy. Further testing of the program will be needed in other population groups to determine a more general applicability.

PEDIATRIC CARDIOLOGY

1175 Management of Surgical Complete Atrioventricular Block in Children

DAVID J. DRISCOLL, PAUL C. GILLETTE, GRADY L. HALLMAN, DENTON A. COOLEY and DAN G. McNAMARA

Complete atrioventricular (A-V) block, a recognized complication of the intracardiac repair of congenital heart defects, may be transient or permanent. In a study of 34 children with this complication complete heart block developed within 24 hours of operation in 28 and later than 1 day after operation in 6. Intracardiac electrophysiologic studies in 14 of the 34 children proved important in the clinical management of this lesion. Permanent pacemaker implantation is indicated if surgically induced complete A-V heart block persists longer than 2 weeks postoperatively and if the site of the block is within or below the bundle of His.

1181 The Fast-Slow Form of Atrioventricular Nodal Reentrant Tachycardia in Children

GRACE S. WOLFF, RUEY J. SUNG, ARTHUR PICKOFF, OTTO L. GARCIA, ROBERT WERBLIN, PEDRO L. FERRER, DOLORES TAMER and HENRY GELBAND

During the electrophysiologic study of two children with resistant supraventricular tachycardia an unusual form of atrioventricular nodal entry characterized by a fast pathway for anterograde conduction and a slow pathway for retrograde conduction was demonstrated with the use of the ventricular extrastimulus technique. A superior axis of the P wave and a P-R/R-P ratio of less than 1 during tachycardia support this fast-slow form of reentrant tachycardia and help to distinguish it from a supraventricular tachycardia involving a concealed accessory pathway for retrograde (fast) conduction where this ratio exceeds 1.

Continued on page A21

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REVIEWS

1189 Left Ventricular Radius to Wall Thickness Ratio

WILLIAM H. GAASCH

The data in this review article emphasize the potential clinical utility of the radius/wall thickness ratio of the left ventricle in numerous cardiac conditions. For example, the normal ratio (3.0 ± 0.7) is found in the physiologic cardiac hypertrophy of the trained athlete and in the patient with compensated chronic aortic regurgitation. An increased ratio conveys a poor prognosis in patients with chronic aortic regurgitation and in those with congestive cardiomyopathy. The ratio is decreased in compensated aortic stenosis. However, small measurement errors, often unavoidable with current methods of measuring left ventricular radius and wall thickness, potentially limit the extensive use of the ratio in clinical cardiology.

SEMINAR ON THROMBOSIS

1195 Introduction

JACOB I. HAFT

1197 Role of Blood Platelets in Coronary Artery Disease

JACOB I. HAFT

This review reports on the latest theoretical and experimental bases for the platelet hypothesis in the pathogenesis and complications of coronary artery disease and the current data on the preventive use of antiplatelet drugs in patients with coronary disease. Although the indications for the use of these drugs in patients with coronary disease have not yet been proved beyond reasonable doubt, the data tend to indicate that antiplatelet aggregating drugs exert a beneficial effect. It appears prudent and worthwhile to use the following drugs and dosages when an antiplatelet aggregation effect is the aim of therapy: aspirin, 325 mg two to three times daily; sulfinpyrazone, 200 mg four times daily; dipyridamole, 50 mg four times daily; propranolol, 20 mg four times daily.

1207 Anticoagulation in Myocardial Infarction: Modern Approach to an Old Problem

WILLIAM H. FRISHMAN and HILLEL S. RIBNER

This review finds little evidence to support the use of long-term anticoagulation therapy to prevent the risks of pulmonary and peripheral emboli in patients after the acute phase of myocardial infarction. Small dose heparin therapy provides an excellent alternative to conventional anticoagulation when there is more than a negligible risk of hemorrhage, as in patients with severe hypertension, prior gastrointestinal bleeding, carcinoma or advanced age. In such patients small dose heparin therapy appears to reduce the incidence of venous thrombosis and probably of pulmonary emboli. Its value in preventing peripheral arterial embolization has not been defined. Rational use of anticoagulation therapy in the setting of acute myocardial infarction may save more than 8,000 lives a year in this country.

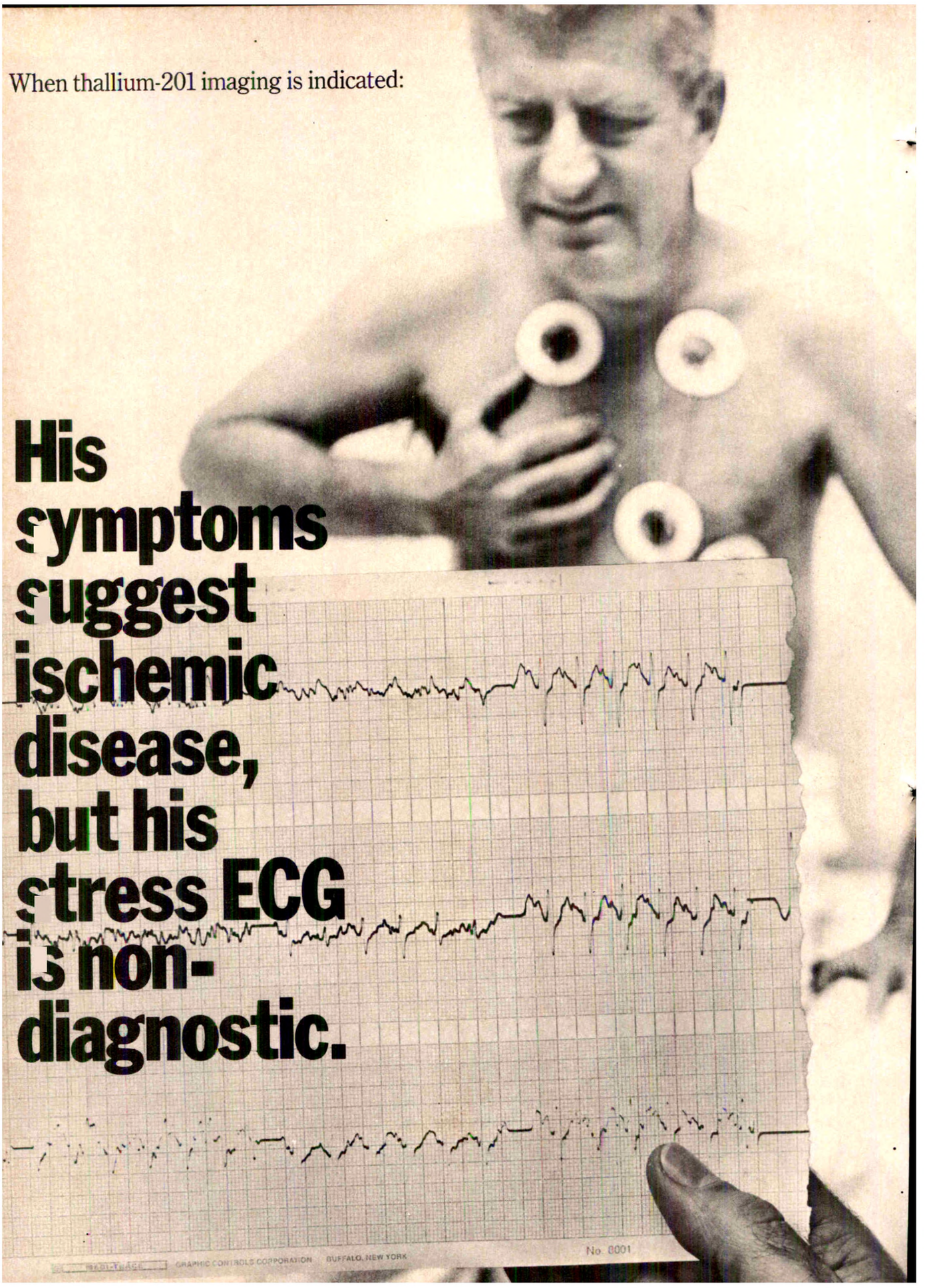
1214 New Developments in the Detection and Prevention of Venous Thromboembolism

ARTHUR A. SASAHARA, G.V.R.K. SHARMA and ALFRED F. PARISI

Although Doppler ultrasonic studies and the radioactive fibrinogen leg scan have been extensively investigated as tools for detecting deep vein thrombosis, the more recently introduced procedure of electrical impedance plethysmography is gaining acceptance as the single best test for its detection. This test shows that a significant number of patients with established deep vein thromboses are asymptomatic (in this series, at least 60 percent). In 95 percent of patients with angiographically confirmed pulmonary embolism, results of impedance plethysmography were abnormal. Subcutaneous small dose heparin therapy to prevent venous thrombosis is effective

Continued on page A25

When thallium-201 imaging is indicated:



His symptoms suggest ischemic disease, but his stress ECG is non-diagnostic.

Approximately 30% of patients with documented coronary artery disease have false-negative stress tests.[1,2] Angiography can demonstrate clinically significant disease in symptomatic patients without stress ECG evidence of myocardial ischemia...but many physicians do not routinely refer these patients for cardiac catheterization. In such settings, clinicians can appreciate the need for a sensitive noninvasive diagnostic alternative to angiography.

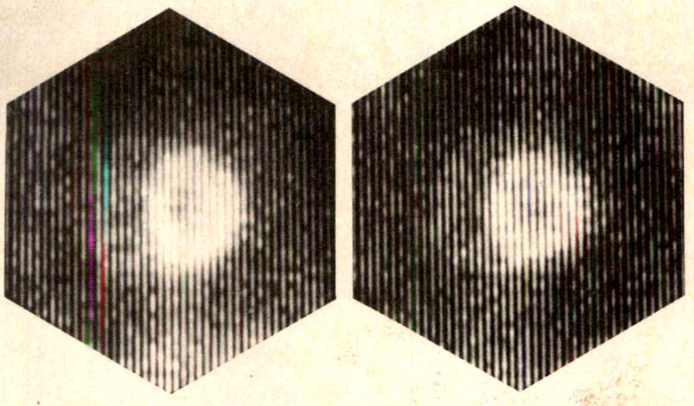
Thallium-201 myocardial imaging, performed as an adjunct to stress electrocardiography, can reliably detect regions of abnormal myocardial perfusion. Intravenously injected thallium-201 is taken up like potassium and concentrated most avidly by normal, well-perfused myocardial cells. Ischemic myocardial cells take up proportionally less thallium-201—particularly during maximal stress, when the differential in perfusion is most marked between regions supplied by normal coronary arteries and those supplied by stenotic vessels. Routinely available nuclear medicine imaging equipment can record these regional differences in thallium-201 uptake, thus documenting the presence or absence of stenotic disease, even in the face of a nondiagnostic stress ECG.

When angiography is not clearly the next step, consider adding thallium-201 imaging to your patients' stress ECG procedures. A growing body of clinical research and experience has demonstrated that the thallium-201 study can:

- detect single-vessel disease in advance of measurable electrocardiographic evidence[3]
- increase the sensitivity and specificity of the stress ECG, particularly in patients where ECG findings and symptomatology do not agree[4,5,6]
- identify those patients with clinically significant but ECG-undefined stenotic disease—patients who will clearly need angiographic evaluation[6]

Unlike angiography, which displays the static anatomic details of the major coronary vessels, the stress thallium-201 study directly demonstrates regional myocardial blood flow and the cellular response to coronary stenosis in a dynamic manner. Redistribution of thallium occurs into regions of stress-induced reversible ischemia of viable myocardium, but not into regions of previous scar formation. For patients in whom the need for angiography has not clearly been defined, the findings of a stress thallium-201 myocardial perfusion study may either rule out significant coronary stenosis, or provide a sound clinical basis for more invasive diagnostic evaluation.[6]

1. Bartel AG et al: Graded exercise stress test in angiographically documented coronary artery disease. *Circulation* **49**:348, 1974.
2. Goldschlager N et al: Treadmill stress tests as indicators of presence and severity of coronary artery disease. *Ann Intern Med* **85**:277, 1976.
3. Bailey IK et al: Thallium-201 myocardial perfusion imaging at rest and during exercise. Comparative sensitivity to electrocardiography in coronary artery disease. *Circulation* **55**:79, 1977.
4. Blood DK et al: Comparison of thallium-201 myocardial scans at rest with scans four hours after exercise. *Circulation* **56** (suppl 3):229, 1977.
5. Raphael LD et al: Thallium exercise myocardial scintigraphy in patients with "angina and normal coronary arteriograms" (abs). *Circulation* **53-54** (suppl 2):217, 1976.
6. Ritchie JL et al: Myocardial imaging with thallium-201 at rest and during exercise. Comparison with coronary arteriography and resting and stress electrocardiography. *Circulation* **56**:66, 1977.



Normal thallium-201 myocardial perfusion images in a 40-year-old man with exertional chest pain and 1-mm ST depression on stress ECG. Images read as "no significant coronary disease." (LAO images: left, immediately postexercise; right, 3 hr postexercise.)

Thallous Chloride Tl 201

NEN New England Nuclear®

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Thallous Chloride Tl 201

For Diagnostic Use

November 1977

Indications and Usage: Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction. It may also be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).

Contraindications: None known.

Warnings: In studying patients in whom myocardial infarction or ischemia is known or suspected, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedure. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

Ideally, examinations using radiopharmaceutical drug products—especially those elective in nature—of women of childbearing capability should be performed during the first ten days following the onset of menses.

Precautions: Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of thallium Tl 201 scans. Attention is directed to the fact that thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the thallium may likewise be affected.

Thallous Chloride Tl 201, as all radioactive materials, must be handled with care and used with appropriate safety measures to minimize external radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to patients in a manner consistent with proper patient management.

No long-term animal studies have been performed to evaluate carcinogenic potential.

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Thallous Chloride Tl 201 should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule nursing should not be undertaken when a patient is administered radioactive material.

Safety and effectiveness in children have not been established.

Adverse Reactions: Adverse reactions related to use of this agent have not been reported to date.

Dosage and Administration: The recommended adult (70kg) dose of Thallous Chloride Tl 201 is 1-1.5mCi. Thallous Chloride Tl 201 is intended for intravenous administration only.

For patients undergoing resting thallium studies, imaging is optimally begun within 10-20 minutes after injection. Several investigators have reported improved myocardial-to-background ratios when patients are injected in the fasting state, in an upright posture, or after briefly ambulating.

Best results with thallium imaging performed in conjunction with exercise stress testing appear to be obtained if the thallium is administered when the patient reaches maximum stress and when the stress is continued for 30 seconds to one minute after injection. Imaging should begin within ten minutes post-injection since target-to-background ratio is optimum by that time. Several investigators have reported significant decreases in the target-to-background ratios of lesions attributable to transient ischemia by two hours after the completion of stress testing.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used by persons with specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agencies authorized to license the use of radionuclides.

How Supplied: Thallous Chloride Tl 201 for intravenous administration is supplied as a sterile, non-pyrogenic solution containing at calibration time, 1mCi/ml of Thallous Tl 201, 9mg/ml sodium chloride, and 9mg/ml of benzyl alcohol. The pH is adjusted to between 4.5-6.5 with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 1.5, 3.0, 4.5, 6.0, and 9.0 millicuries of Thallous Tl 201.

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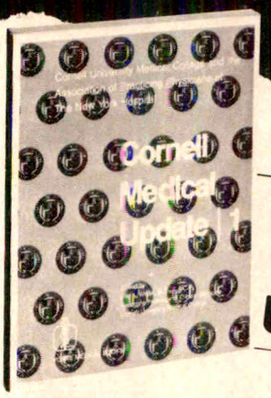
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DIAGNOSTIC SHELF

1225 Noninvasive Visualization of Coronary Arterial Aneurysm in Infants and Young Children With Mucocutaneous Lymph Node Syndrome With Two Dimensional Echocardiography

SATOSHI HIRAISHI, KIMIO YASHIRO and SHOICHI KUSANO

Arteritis, myocarditis, pericarditis and coronary aneurysms may be found in the mucocutaneous lymph node syndrome, which most frequently affects infants and children less than 5 years of age. These investigators successfully visualized the main coronary arteries using an electronic linear two dimensional echocardiographic technique in 30 normal infants and children and in 58 patients with the mucocutaneous lymph node syndrome. In 7 of these 58 patients with this syndrome, a portion of the left main coronary artery had a fusiform or a spherical pattern, or both, and the stem of the right coronary artery also had a spherical pattern in 2 patients. In all five patients who had coronary angiography, this procedure confirmed the echocardiographic finding of an aneurysm. These results confirm that two dimensional echocardiography is a reliable noninvasive method for detecting coronary arterial aneurysms in infants and young children.

CASE REPORTS

1234 Sucking Action of the Left Ventricle: Demonstration of a Physiologic Principle by a Gunshot Wound Penetrating Only the Right Side of the Heart

WILLIAM C. ROBERTS, WILLIAM J. BROWNLEE, ANCIL A. JONES and JAMES L. LUKE

At necropsy, the left atrial appendage was found inverted and invaginated into the mitral orifice of a man who died after a gunshot wound that entered the right atrium and exited from the right ventricle without entering the cardiac septa or the left side of the heart. This evidence suggests that the human left ventricle does have the capacity under certain circumstances to create a negative pressure and to suck blood into it from the left atrium. Previously reported experiments in animals demonstrating the sucking (negative pressure) action of the left ventricle during ventricular diastole are also summarized in this report.

1238 Fatal Acute Bacterial Myocarditis After Dentoalveolar Abscess

EDWARD A. PALANK, MODUR L. JANARDHANA and MILTON UTELL

This unusual case of a 19 year woman with chest pain after a dental extraction for a dentoalveolar abscess demonstrates the need to suspect infective myocarditis in young patients who present with clinical signs of myocardial infarction. Autopsy revealed isolated acute bacterial myocarditis and three distinct organisms in the myocardium in the absence of endocarditis or a myocardial abscess. These bacteria were believed representative of those cultured in the antemortem blood.

EDITORIALS

1242 Hypertrophic Cardiomyopathy: A Discussion of Nomenclature

BARRY J. MARON and STEPHEN E. EPSTEIN

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1245 **Variant Angina: More Variants of the Variant**
SAMUEL J. SHUBROOKS, Jr.

SPECIAL DEPARTMENTS

1249 **American College of Cardiology News**

1258 **Author Index: Volume 43**

1260 **Subject Index: Volume 43**

CORRECTION

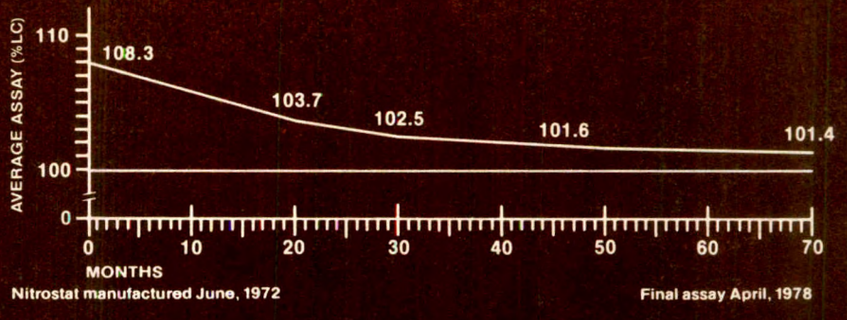
The following editorial was inadvertently omitted from the April table of contents: Rosen KM, Bauernfeind RA, Wyndham CR, Dhingra RC: Retrograde properties of the fast pathway in patients with paroxysmal atrioventricular nodal reentrant tachycardia. Am J Cardiol 43: 863–865, 1979

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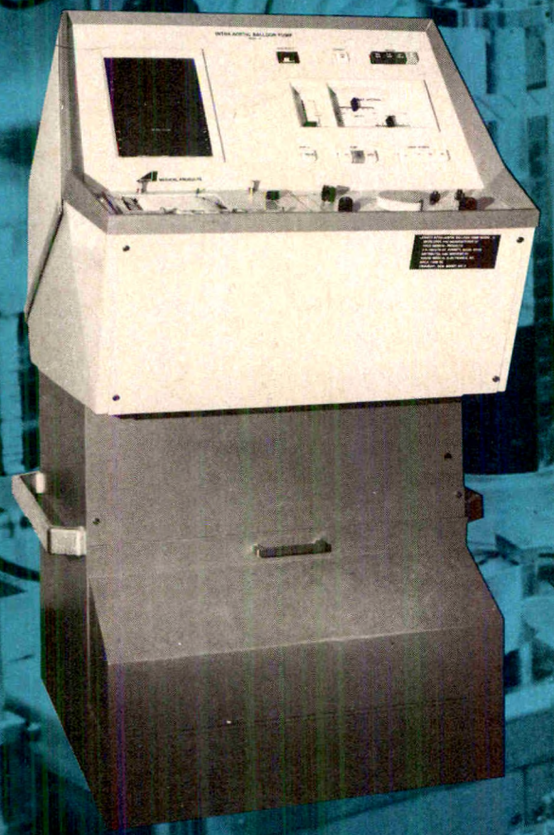
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AJC-6/79

2-1624

The featured product in this photograph is the Quinton Model 623 ECG Monitoring System. It is designed to enable a physician or clinic to start a moderately sophisticated stress test program at a reasonable cost. The 623 offers a basic two-channel, seven-lead unit with features such as a two-channel monitoring scope, dual-channel recorder, push-button lead selection, heartrate meter, patient isolation system, defibrillator protection and complete system calibration. Interfacing with the 623 is a family of optional equipment designed to provide additional test capabilities. This equipment can be added economically, as needed, component by component. These options include the Quinton treadmill programmer and the ECG data computer which records and displays four separate S-T functions.

The 623 and other members of the Quinton family of exercise electronics are complimented by the world's finest treadmill. Quinton led the way with the first — and still most popular treadmill — engineered to meet the specific needs of cardio-pulmonary function testing. The challenge of leadership in the treadmill field led naturally to the development of a family of quality stress test electronics to provide the medical field with the total system it needed.

So — if you're looking at stress test systems, look to the leader! Quinton can help you develop a total system, integrating exercise and electronics equipment precisely to your needs today — with the capability to grow for tomorrow. We'll show you why you can't beat the system!

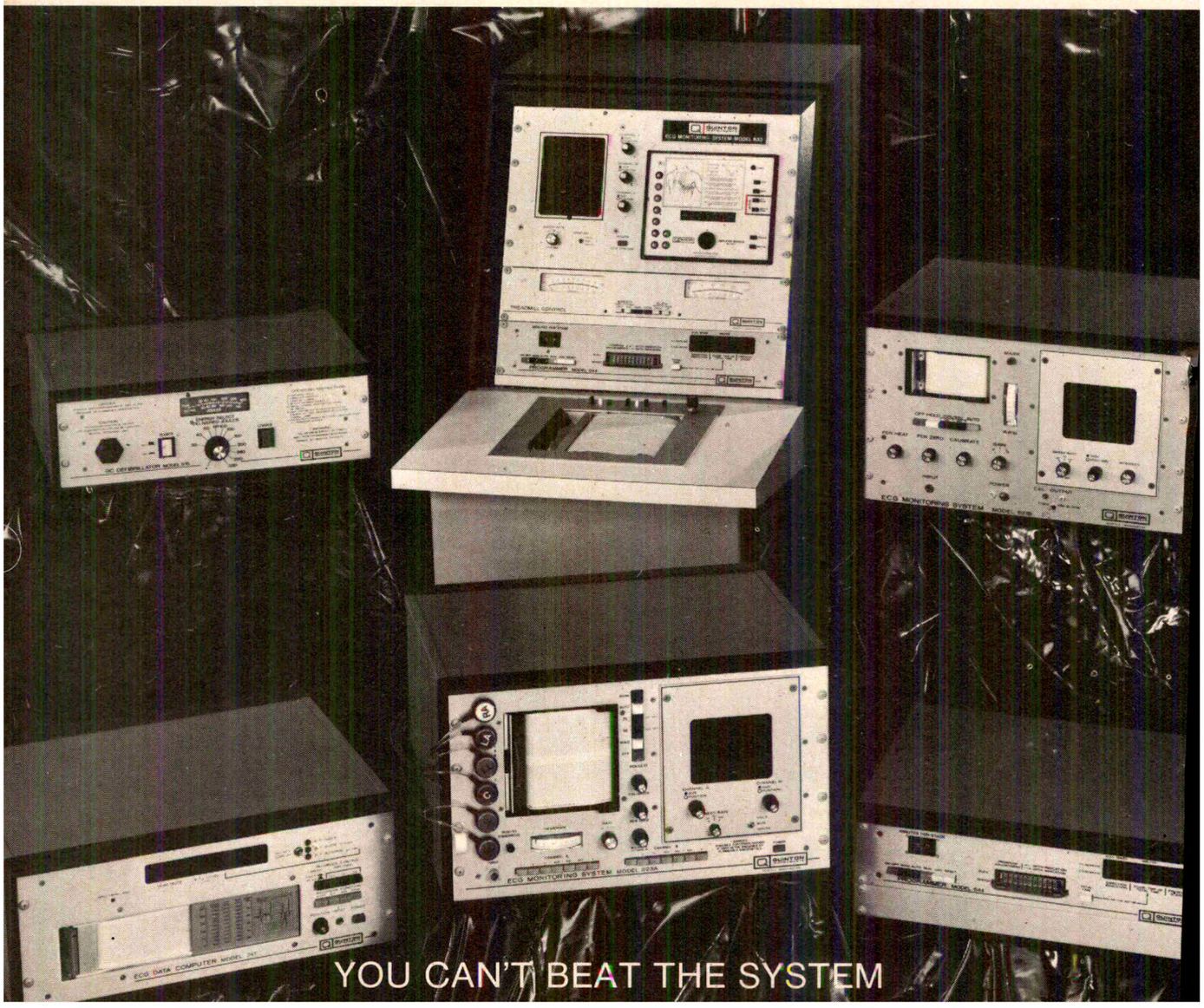
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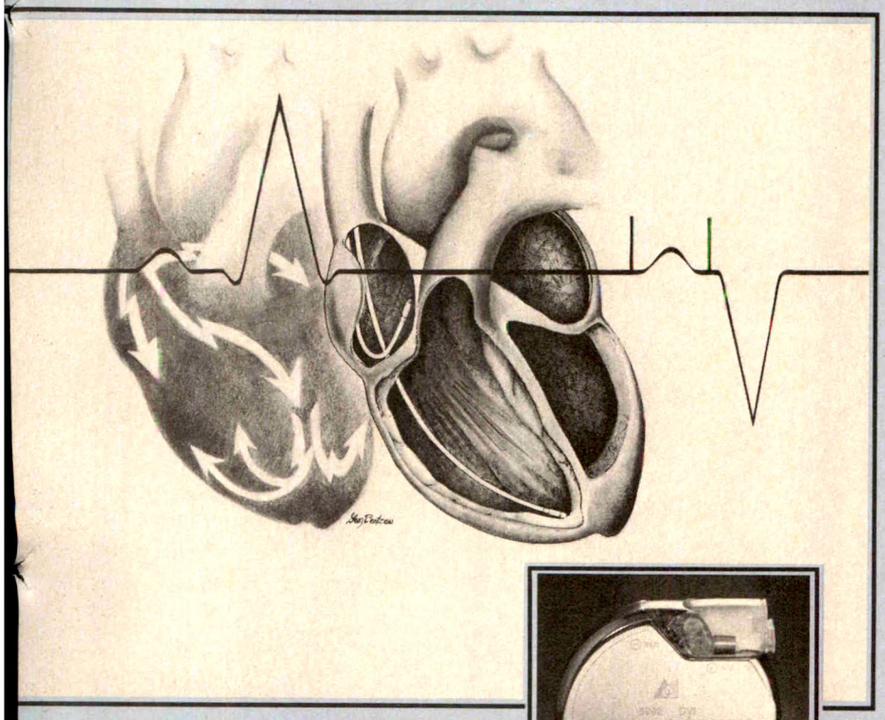
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Pacing News

A PHYSICIAN SERVICE OF MEDTRONIC, INCORPORATED VOL. 1, NO. 1

Medtronic Unfolds
NEW A-V SEQUENTIAL PACEMAKER





edtronic's new Byrel™ implantable pacemaker
esigned for A-V sequential pacing.

Both temporary and permanent A-V sequential pacing are likely to see more frequent applications because of two new products recently developed by Medtronic, Inc., Minneapolis, Minn. These products are the Byrel™ implantable A-V sequential pacemaker and the Model 5330 external A-V sequential pacemaker.

Interest in A-V pacing is growing because of this pacing mode's potential for both improving cardiac output and for control of certain tachyarrhythmias.

Restoration of A-V synchrony can improve cardiac output by providing regular atrial filling of the ventricles and by providing more normal valve function in some patients.

It may also prevent retrograde pumping by the atria and increase the efficiency of myocardial oxygen use (when compared to ventricular pacing).

A-V sequential pacing will also prevent most forms of retrograde atrial stimulation and bradycardia.

Controlled A-V synchrony provides a method for management of certain tachyarrhythmias preventing the long PR intervals necessary for some of the re-entry tachyarrhythmias. Of course, it can also prevent atrial bradycardia in brady-tachy syndrome and drug-induced bradycardia. A-V sequential pacing can also overdrive ventricular arrhythmias while providing the bene-

A-V SEQUENTIAL continued on page 2

yrel® and Xyrel®-VP Pacemakers Earn 99.9% Performance Rating

Medtronic's Xyrel® and Xyrel®-VP cemakers are daily setting new reliility records at Medtronic, earning a rformance index of 99.9%. That eans that 99.9% of these products can expected to perform within specifican over the next six-month period.

To-date, nearly 73,000 Xyrel® pacekers have been sold in the U.S.—acmulating in the past three years arly three-quarters of a million imnt device months.

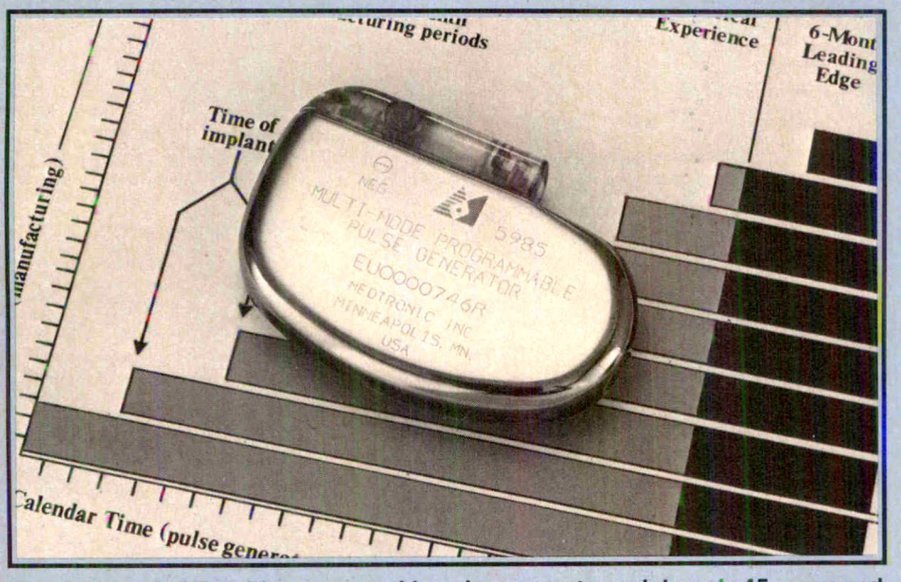
Yet, the number of units verified to be of specification when returned to Medtronic is extremely low—only 18 actual "out of spec" units have been observed by Medtronic technicians. Thus, the current performance index for both the Xyrel® and the Xyrel® -VP units is 99.9%.

The Medtronic Performance Index is a patient management tool developed by the company to provide up-to-date device performance information for the physician. Its unique value is that it is not diluted by early, historical product experience and it covers only presently implanted devices.

Of the total Xyrel® pacemakers sold, about 13,000 have consisted of Xyrel®-VP ventricular programmable units. Of these, only one has been observed to have a component failure by Medtronic technicians.

The performance index for each individual pacemaker is reported quarterly to the physician with Medtronic's Implant Data Report. Ask your Medtronic representative for a brochure giving details of the Medtronic Performance Index, or send in the coupon following Product Information Summary.

Spectrax™ Pacemaker in Clinical



The Spectrax™-SX multi-programmable pulse generator weighs only 45 grams and has a volume of 21 cc.

The new Spectrax™-SX multi-programmable pacemaker is now undergoing clinical evaluation. The first implant was performed on a 44-year-old man in Miami, Fla., in November, 1978. The investigation has been expanded to other centers across the country.

"Whenever a new pacing product is being developed, it creates interest in the medical community," says Spectrax™ marketing manager, Dennis Sellke. "But, Medtronic's Spectrax™ pacemaker, because of the flexibility built into its programmable modes and functions, has generated early and unusually high excitement. The Spectrax™ pacemaker represents significant and important technological progress in pacing," Sellke says.

Using the most modern micro-processor technology, the Spectrax™-SX pacemaker will offer the physician atrial or ventricular asynchronous, atrial or ventricular inhibited, and atrial or ventricular triggered modes. This pacemaker's several programmable parameters include pacing rate (30 to 150 beats per minute), pulse width (.05 to 2.0 msec) amplitude, sensitivity, refractory and hysteresis.

A-V SEQUENTIAL continued

fits of improved cardiac output.

Making these benefits available to the physician and his patient are Medtronic's A-V sequential pacing products. Leading off is the new Byrel™ a programmable, lithium-powered, ventricular-inhibited device with seven A-V programs and one ventricular-inhibited mode (atrial unit shut-down).

The Byrel™ has many of the performance features of other Medtronic pulse generators, including a lithium power source, titanium external covering, hermetically sealed hybrid electronics and more. Of course, both atrial and ventricular leads are required.

A companion to the Byrel™ is Medtronic's new 5330 external pacemaker designed for temporary atrial, ventricular or A-V sequential pacing.

In addition to its use in temporary pacing and diagnostic applications, you can also measure atrial or ventricular current stimulation thresholds with the 5330. It can also approximate R-Wave potentials sensed via ventricular pacing lead electrodes.

Amplitude of atrial and ventricular output pulses is set separately by individual controls. You can also adjust ventricular sensitivity, ventricular rate and A-V interval.

LEADS

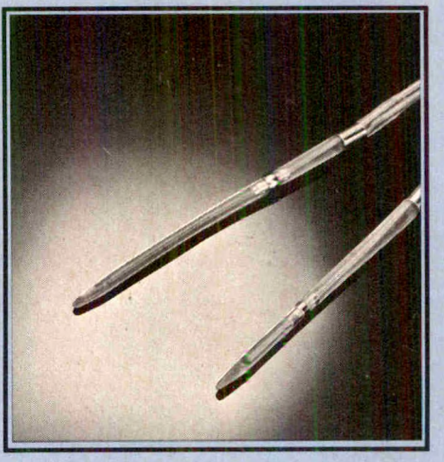
Atrial pacing requires leads designed to deal effectively with the insertion and dislodgement problems of atrial placement. Three J-shaped leads (Models 6990 bipolar, 6991 unipolar and 6994 bipolar) facilitate placement and stable electrode placement in the right atrial appendage. Two coronary sinus bipolar endocardial leads (Models 6992 and 6992A) are designed for placement in the coronary sinus for permanent atrial pacing and sensing applications. The electrode configuration of the 6992A, 6990 and 6994 is specifically designed for enhancement of A-V sequential pacing.

Medtronic also provides a temporary disposable bipolar lead (Temptron Model 6705). It features a needle/introducer designed for easier handling during venous introduction. Its "push button," detachable connector permits complete removal of the percutaneous introducer cannula. This lead has been used for atrial pacing from the coronary sinus and ventricular pacing from the right ventricular apex.

Since A-V sequential pacing does not depend on a functional A-V conduction system, there are no major contraindications to this mode of therapy.



Model 5330 external pacemaker for atrial, ventricular or A-V sequential pacing.



Implantable atrial pacing leads. The unit with the short electrode spacing (6992A) is designed for A-V sequential pacing.

Medtronic Helping you help the pacemaker patient

FOR FURTHER INFORMATION SEND IN COUPON AT RIGHT.

MEDTRONIC® PRODUCT INFORMATION SUMMARY

Medtronic® External Pacing Products

Intended Use—The Model 5330 external pulse generator is intended for use with pacing lead systems for temporary cardiac pacing where such procedures are indicated for therapeutic, prophylactic or diagnostic purposes. The Model 5330 may be used for temporary atrial, ventricular or A-V sequential pacing.
Contraindications—Atrial pacing should be used only in patients with intact A-V conduction systems. The existence of anomalous conduction pathways bypassing normal A-V conduction is a potential contraindication for atrial stimulation. In the A-V sequential pacing mode, use of the Model 5330 with certain implanted lead systems may be contraindicated. See the 5330 technical manual for more information.
Warnings—All electrical equipment that is used invasively or attached to a pacing lead system increases the patient's chances of exposure to potentially hazardous leakage currents. For complete information on the quality and degree of such exposure, consult the technical literature supplied with each product.
Precautions—All man-made devices are subject to malfunction. Appropriate standby equipment should be immediately available when temporary pacing is employed.
Potential Complications—Major potential complications related to temporary pacing are asystole following abrupt cessation of pacing and lead-system-related problems. Atrial stimulation carries, in addition, the potential complication of accidental high-rate ventricular stimulation possibly resulting in ventricular tachycardia or fibrillation.

Medtronic® Implantable Pulse Generators

Intended Uses—Ventricular pacing using an implantable ventricular pulse generator and lead system are for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems. Cardiac pacing using an implantable A-V sequential pulse generator is for long-term therapeutic control of heart rate in patients where restoration of A-V synchrony is indicated to improve cardiac output or to protect against arrhythmias related to sequence of cardiac impulse propagation.
Contraindications—There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.
Warnings—Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.
Precautions—The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.
Side Effects—Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

Medtronic® Implantable Pacing Leads and Accessories

Intended Use—Medtronic® implantable pacing leads are designed to be used with Medtronic® pulse generators as part of a cardiac pacing system (see product labeling for specific directions regarding applications).
Contraindications—Endocardial pacing leads are contraindicated in the presence of tricuspid valvular disease.
Warnings—An implanted lead or lead/adaptor combination constitutes a direct, low resistance current path to the myocardium. During the connection and testing procedures, only battery-powered pulse generators should be used with the lead system to protect against ventricular fibrillation induced by alternating current leakage. Extreme caution must be taken to properly ground all line-powered equipment used in the vicinity of the patient. Lead adaptors, lead extenders and repair kits should not be used if the integrity of the lead is in doubt.
Precautions—The pacing system may cease to function due to lead-related problems such as displacement, fracture, fibrotic tissue formation and elevated thresholds.
Side Effects—Body rejection phenomena, infection, erosion or migration through body tissue, transvenous lead-related thrombosis, embolism.
How Supplied—Medtronic® permanent implantable leads and accessories are supplied sterilized and, in most cases, individually packaged.

I would like more information on:

- ☐ A-V sequential pacing products
- ☐ Xyrel®-VP Performance
- ☐ The Mirel™ Pulse Generator
- ☐ Other _____

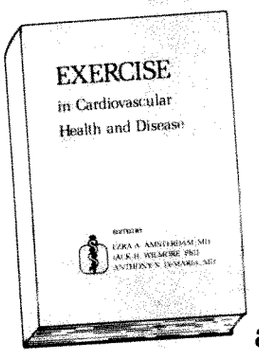
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EXERCISE in Cardiovascular Health and Disease

Edited by
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Jack H. Wilmore, PhD, Professor and Head Dept of Physical Education & Athletics, Univ. Arizona
Anthony N. DeMaria, MD, Dir. Echocardiography Section, Univ. of Calif. School of Medicine

SEPTEMBER 1977, 408 PAGES, ILLUS.

Just published, this comprehensive work covers every aspect of exercise and its role in **Diagnosis, Treatment,** and **Prevention** of cardiac disease.

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INTRODUCING THE 80 MG TABLET LASIX® (furosemide)

In the course of cardiac edema a patient may need more than the usual 40 mg dose of Lasix.® It is for this patient that we formulated the new Lasix 80 mg tablet.

Impaired renal function—associated with the more severe degrees of congestive heart failure—can greatly reduce the effectiveness of diuretic therapy. What is often required to provide effective saluresis for such patients is a loop diuretic.

The new Lasix 80 mg provides a convenient dosage unit to achieve the necessary saluresis. And, it offers greater patient compliance and can result in significant savings.

Lasix Tablets Prescribing Guide Usual adult daily dose: 20 to 80 mg given in morning. Dosage may be increased by increments of 20 to 40 mg not sooner than 6 to 8 hours after previous dose. May be carefully titrated up to 600 mg/day in severe clinical edema patients. Therapy should be individualized according to patient response. As with any diuretic, electrolyte depletion can occur during therapy with furosemide. When doses exceeding 80 mg/day are given for prolonged periods, careful clinical and laboratory observations are recommended.

Please consult brief summary of prescribing information below.

Lasix® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide) Tablets 20, 40 and 80 mg

Warning: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone

Contraindications: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

Warnings: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

Precautions: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when

BECAUSE IN CARDIAC EDEMA... THERE IS A POINT AT WHICH A GOOD DRUG BECOMES AN INVALUABLE ONE.



the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

Adverse Reactions: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice, (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

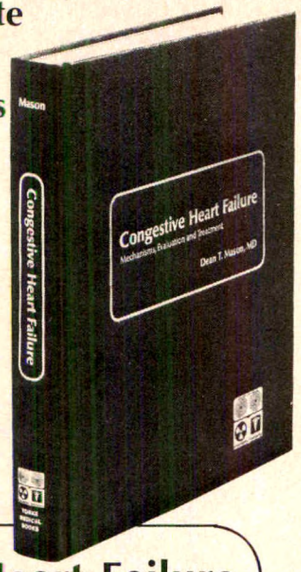
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Congestive Heart Failure

Mechanisms, Evaluation and Treatment
Dean T. Mason, M.D.

This rare treatment of such a multifaceted subject provides an unusual opportunity for the busy clinician to add to his knowledge in a minimum amount of time. Any area of immediate interest can be rapidly located and as much data as needed can be quickly extracted. The concentration on improved clinical management will be appreciated by every internist, cardiologist, generalist, and any professional involved in cardiovascular medicine.

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This presentation of recent advances in basic research and clinical progress has been highly acclaimed for its major contribution to the improvement of patient care. We invite you to see if you don't agree. Order and take 30 days to look over the book. If you're not totally satisfied, return it.

About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis.

President, American College of Cardiology; President, Western Society for Clinical Research.

Member of the American Board of Internal Medicine Cardiovascular Diseases.

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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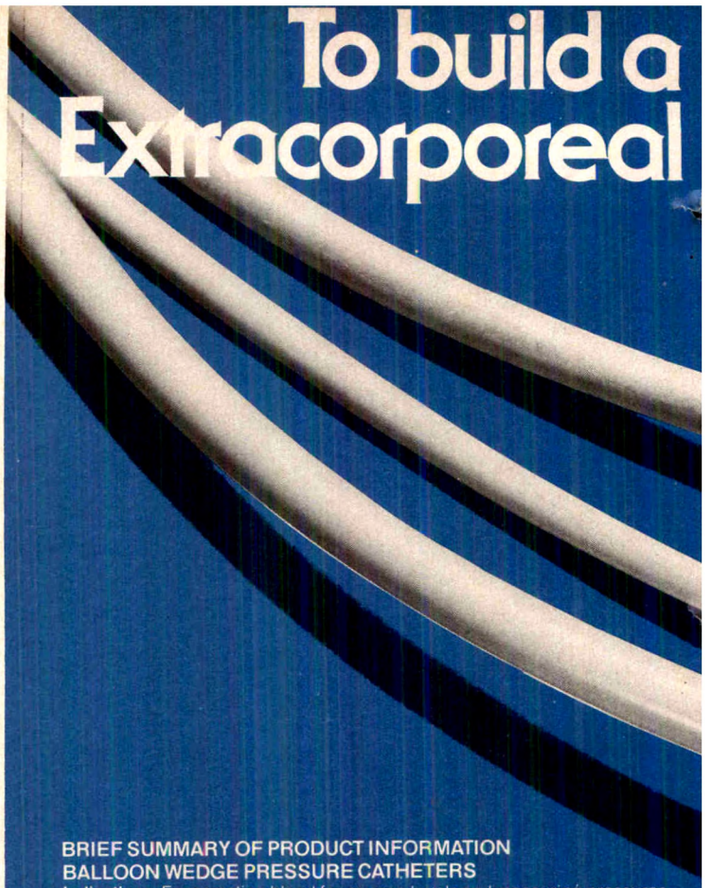
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To build a Extracorporeal



BRIEF SUMMARY OF PRODUCT INFORMATION
BALLOON WEDGE PRESSURE CATHETERS

Indications: For sampling blood for oxygen levels and measuring pressures in the right heart, including central venous, right ventricular, pulmonary artery, and pulmonary artery wedge pressure. Also indicated in anatomical cardiac defect cases to sample blood and measure pressures in any chambers that can be entered from the right heart. **Warning:** Pulmonary artery perforation, thrombosis, segmental pulmonary infarction, transient obstruction of the pulmonary outflow by the inflated balloon, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of the catheter have been reported as complications of the use of balloon catheters. Balloon rupture with possible latex embolus is a potential complication in the use of balloon catheters. **Precaution:** In pressure monitoring at bedside when catheter has been introduced in an antecubital vein, patient's arm should be immobilized to reduce the possibility of catheter advancement due to arm motion.

BERMAN ANGIOGRAPHIC CATHETER

Indications: For use in right-heart catheterization for cardiac angiography, pulmonary angiography, and measurement of right-heart and pulmonary artery pressures. It can be used to inject radiopaque media and measure pressures in any chambers and vessels that can be entered from the right heart. **Warnings:** Angiograms should be done with balloon inflated to minimize myocardial staining. When injecting radiopaque media, do not exceed stated maximum flow rate and pressure. Transient obstruction of the pulmonary outflow tract, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of catheters are reported complications of the use of balloon catheters. Balloon rupture with possible latex embolus is a potential complication in the use of balloon catheters. **Precaution:** Manipulate catheter carefully and gently to avoid kinking or knotting.

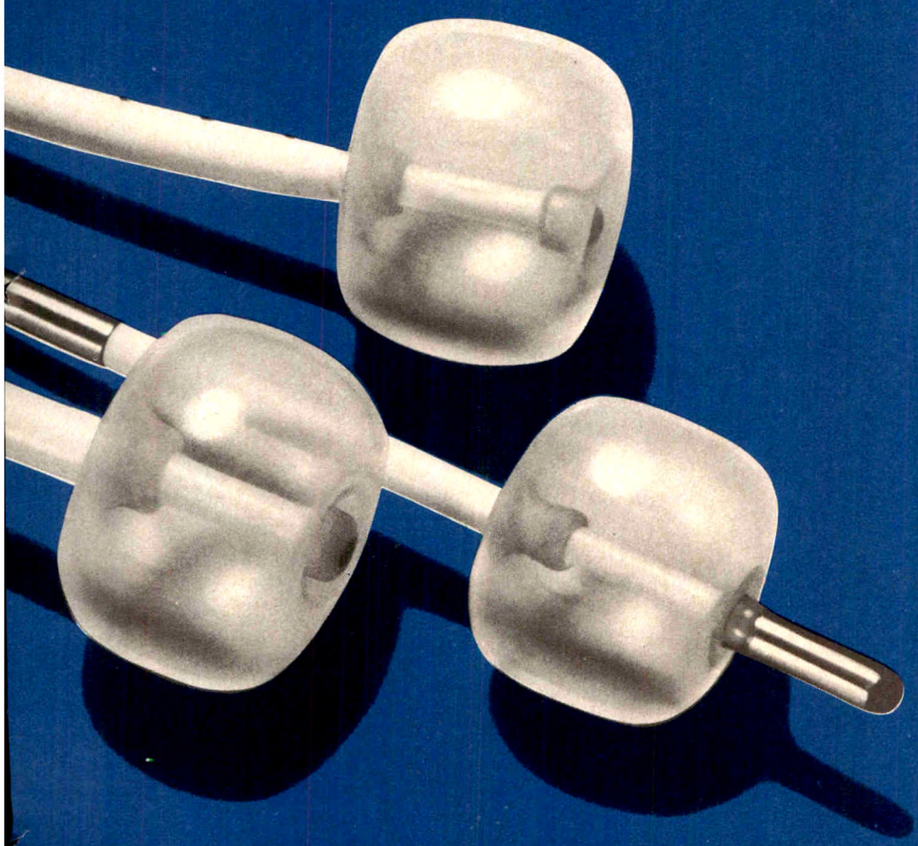
BIPOLAR TEMPORARY PACING W/STYLET AND BALLOON TEMPORARY PACING CATHETERS

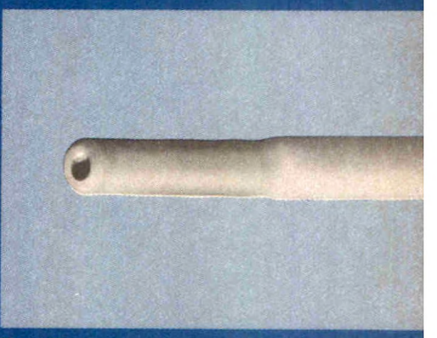
Indications: For temporary transvenous cardiac pacing when impulse formation or conduction is impaired. **Warnings:** Myocardial perforation, fibrillation and arrhythmia, pulmonary embolism, thrombus formation, and infection are general complications of transvenous pacing. Balloon rupture with possible latex embolus, vessel perforation, and intimal disruption are potential complications of use of balloon temporary pacing catheters. With the transbrachial approach, malpositioning and perforation occur more frequently due to arm movement. Pneumothorax, air embolism, and puncture of the subclavian artery have been reported with the subclavian approach. **Precautions:** Avoid kinking or bending catheter to prevent damage to internal wires or occlusion of inflation lumen (in balloon pacing catheter). Maintain insertion site with regular meticulous redressing performed with aseptic technique. Remove stylet from Bipolar Pacing Catheter after it is in position because leaving stylet *in situ* increases the potential for perforation.

FOR BALLOON CATHETER USE, IN GENERAL

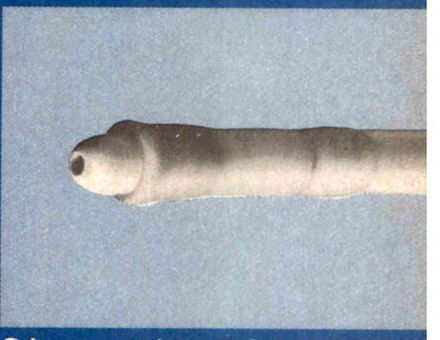
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The interview excerpted here was conducted with Glen W. Hamilton, M.D., Chief, Nuclear Medicine Section, Veteran's Administration Hospital, Seattle, Washington. Dr. Hamilton is also an Associate Professor of Medicine, University of Washington School of Medicine.

Q. Of the nuclear cardiology studies available in clinical practice today, which are the most difficult to interpret?

A. Thallium images are probably the most difficult to interpret, and pyrophosphate are probably the next. In about 60% of all abnormal studies, the abnormality is quite obvious. The remaining 40% are quite difficult to read. As the physician gains experience, he will be able to read about half of those with confidence, but about 20% of all thallium studies remain difficult to interpret. Experienced observers will have legitimate disagreement as to whether a given study is normal or abnormal.

Q. Which of these tests are generally the best in the assessment of left ventricular function? Is this also the best study for assessing wall motion?

A. The multiple gated blood pool study yields the greatest clinical information compared to the difficulty of performing the test and, therefore, is the one we use in our clinical practice when we wish to assess a patient's ventricular function. The best study for assessing wall motion is probably the multiple gated study. It is not perfect, in that the right ventricle and the left ventricle overlap in all but the LAO view...but for most laboratories it is the most practical way to assess wall motion.

Q. What studies would you recommend to a nuclear physician or cardiologist beginning nuclear cardiology in a community hospital?

A. I would recommend two studies: multiple gated blood pool studies, and thallium imaging. The ventricular function measurements obtained from multiple gated studies are useful not only in patients who have suspected coronary disease, but also in a wide variety of other patients, such as people with lung disease, older patients who have undetected ventricular dysfunction, or presurgical patients. Clearly, this is going to be the largest volume study, and that's the place where they should start. After doing resting ventricular function studies, they should progress to thallium imaging. Six months from now, there should be enough data available on rest/exercise ventricular function studies using multiple gated imaging to indicate whether this technique is of general usefulness.

Q. Which studies are most difficult to perform?

A. Pyrophosphate studies are obviously the simplest to perform. The multiple gated blood pool study is performed quite simply. However, the equipment required is not present in every laboratory at the present time. Thallium, being a less ideal isotope, is probably the most difficult study, in terms of the technique required to achieve good diagnostic results.

Q. What may be the single most important use of these nuclear cardiology studies in five years?

A. First, I'm confident we will be noninvasively measuring ventricular function in a wide range of patients with various disease states — coronary artery disease, cardiomyopathy, chronic lung disease, valvular heart disease and many others. We will be able to follow these patients, correctly select the optimal time for surgical intervention, and alter medical therapy so that treatment is optimal. There's no question that this will happen. Secondly, if these tests turn out to be quite sensitive for the detection of coronary artery disease in its early presymptomatic stages, it may be possible to alter that disease by various interventions. This could become a very important national endeavor which could have far-ranging effects on health in this country.

Q. How widespread do you see these techniques becoming?

A. The need for studies of ventricular function will be comparable to the need for lung or bone scans. I really expect that most existing nuclear medicine laboratories, and, generally any hospital of two or three hundred beds, will be able to perform ventricular function studies within the next several years.

For the complete transcript of this interview with Dr. Hamilton, write Inner-View, General Electric Company, Medical Systems Division, P.O. Box 414 (Mail Code W-504), Milwaukee, WI 53201.

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INDICATIONS:

1. Congestive heart failure: Congestive heart failure, all degrees, is the primary indication. The increased cardiac output due to digoxin results in diuresis and general amelioration of the disturbances characteristic of right (venous congestion, edema) and left (dyspnea, orthopnea, cardiac asthma) heart failure.

Digoxin, generally, is most effective in "low output" failure and less effective in "high output" (bronchopulmonary insufficiency, infection, hyperthyroidism) heart failure.

Digoxin should be continued after heart failure is abolished unless some known precipitating factor is corrected.

2. Atrial fibrillation: Atrial fibrillation, especially when the ventricular rate is elevated. Digoxin rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

3. Atrial flutter: Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digoxin at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digoxin if failure ensues or if atrial flutter is a frequent occurrence.

4. Paroxysmal atrial tachycardia: Oral digoxin may be used, especially if the condition is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if heart failure has ensued or paroxysms recur frequently, digoxin should be maintained by oral administration.

Digoxin is not indicated in sinus tachycardia unless due to heart failure.

5. Cardiogenic shock: The drug is often employed, especially when the condition is accompanied by pulmonary edema. Digoxin seems to affect adversely shock due to septicemia from gram-negative bacteria.

CONTRAINDICATIONS: The presence of toxic effects (see ADVERSE REACTIONS section) induced by any digitalis preparation is a contraindication to all of the glycosides.

Allergy, though rare, does occur. It may not extend to all preparations, and another may be tried.

Ventricular fibrillation.

WARNINGS:

> Digitalis alone or with other drugs has been promoted for use in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

Many of the arrhythmias for which digoxin is advised closely resemble those reflecting digoxin intoxication. If the possibility of digoxin intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digoxin intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

Patients with renal insufficiency require smaller than usual doses of digoxin. Newborn infants display considerable variability in their tolerance to digoxin, depending on their degree of maturity.

Premature and immature infants are particularly sensitive, and dosage must be reduced and digitalization should be even more individualized and cautiously approached than in more mature infants. Impaired renal function must also be carefully taken into consideration.

Congestive heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. A relatively low total dose administered in divided doses and concomitant use of antihypertensive drugs has been recommended. ECG monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with rheumatic carditis, especially when severe, are unusually sensitive to digoxin and prone to disturbances of rhythm. If heart failure develops, digitalization may be initiated with relatively low doses; then it can be cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS: Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid digoxin toxicity if digoxin is used to help the arrhythmia.

Digoxin is not indicated for the treatment of ventricular tachycardia unless congestive heart failure supervenes after a protracted episode not itself due to digoxin.

Potassium depletion sensitizes the myocardium to digoxin and toxicity may develop even with usual dosage. Hypokalemia may also alter the rate of onset and intensity of the positive inotropic effect of digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin.

Potassium wastage may result from diuretic or corticosteroid therapy, hemodialysis, and from suction of gastrointestinal secretions. It may accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing congestive heart failure. In general, rapid changes in serum potassium or other electrolytes are to be avoided, and intravenous treatment with potassium should be reserved only for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES section).

Patients with acute myocardial infarction, severe pulmonary disease, or far advanced heart failure may be more sensitive to digoxin and more prone to disturbances of rhythm.

Calcium affects contractility and excitability of the heart in a manner similar to that of digoxin. Calcium may produce serious arrhythmias in digitalized patients.

In myxedema, the digoxin requirements are less because excretion rate is decreased and blood levels are significantly higher.

In incomplete A-V block, especially in patients subject to Stokes-Adams attacks, advanced or complete heart block may develop if digoxin is given. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.

Patients with chronic constrictive pericarditis may respond unfavorably to digoxin.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Renal insufficiency delays the excretion of digoxin and dosage must be adjusted accordingly in patients with renal disease. Note: This applies also to potassium administration should it become necessary.

Electrical conversion of arrhythmias may require reduction of digoxin dosage.

Dosage must be carefully titrated and differences in the bioavailability of parenteral preparations, elixirs, and tablets should be taken into account when switching patients from one preparation to another.

Electrocardiographic monitoring may be necessary to avoid intoxication.

Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

ADVERSE REACTIONS:

Gynecomastia: Uncommon.

Overdose or toxic effects in adults:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea are the most common early symptoms of overdosages in the adult (but rarely conspicuous in infants). Uncontrolled heart failure may also produce such symptoms.

Central nervous system: Visual disturbances (blurred vision, yellow vision), headache, weakness, apathy.

Cardiac disturbances (arrhythmias): Ventricular premature beats are the most common, except in infants and young children. Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (interference) dissociation and paroxysmal atrial tachycardia (PAT) with block are also common arrhythmias due to digoxin overdosage.

Conduction disturbances: Excessive slowing of the pulse is a clinical sign of digoxin overdosage. Atrioventricular block of increasing degree may proceed to complete heart block. Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac toxic disturbances. Digoxin may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

Overdose or toxic effects in children:

Toxic signs differ from the adult in a number of respects. Cardiac arrhythmias are the more reliable and frequent signs of toxicity.

Vomiting and diarrhea, neurologic and visual disturbances are rare as initial signs.

Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.

Atrial arrhythmias, atrial ectopic rhythms, and paroxysmal atrial tachycardia with A-V block particularly are more common manifestations of toxicity in children.

Ventricular arrhythmias are rare.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE: Digoxin should be discontinued until all signs of toxicity are abolished. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.

Potassium salts are commonly used. Potassium chloride in divided oral doses totaling 4-6 grams for adults (see PEDIATRIC INFORMATION section for pediatric dosage) may be given provided renal function is adequate.

When correction of the arrhythmia is urgent and the serum potassium level is low or normal, potassium should be administered intravenously in a solution of 5 percent dextrose in water. A total of 40-100 milliequivalents (30 milliequivalents per 500 milliliters) is given at the rate of 20 milliequivalents per hour unless limited by pain due to local irritation.

Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.

Continuous electrocardiographic monitoring should be performed to watch for any evidence of potassium toxicity, e.g., peaking of T waves, and to observe the effect on the arrhythmia so that the infusion may be promptly stopped when the desired effect is achieved.

Caution: Potassium should not be used and may be dangerous for severe or complete heart block due to digoxin and not related to any tachycardia.

Other agents that have been approved for the treatment of digoxin intoxication include procainamide, lidocaine, and propranolol.

Pediatric Information: (See adult section for other recommendations for the treatment of arrhythmias produced by overdosages and for additional recommendations and cautions regarding the use of potassium.) Potassium preparations may be given orally in divided doses totaling 1-1.5 milliequivalents/kilogram (1 gram K contains 13.4 milliequivalents). When correction of the arrhythmia is urgent, approximately 0.5 milliequivalents/kilogram of potassium per hour may be given, with careful electrocardiographic monitoring, as a solution of 20 milliequivalents or less for 500 milliliters in 5 percent dextrose in water. The total dose should generally not exceed 2 milliequivalents of potassium/kilogram.

DOSAGE AND ADMINISTRATION: Oral digoxin is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. The amount can be predicted approximately from the lean body mass of the patient with allowances made for excretion during the time taken to induce digitalization.

Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.

Recommended dosages are practical average figures that may require considerable modification as dictated by individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended or average doses. (See WARNINGS and PRECAUTIONS sections.)

The average amount of digoxin that patients must accumulate to be digitalized with digoxin tablets is 1.0-1.5 milligrams. Digitalization may be accomplished by any of several approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount accumulated.

In previously undigitalized patients, a single loading dose of 0.5-0.75 milligram orally usually produces a detectable effect in 1-2 hours that becomes maximal in 6-8 hours. Additional doses of 0.25-0.5 milligram may be given cautiously at 6-8 hour intervals to full digitalization.

In previously undigitalized patients, institution of daily maintenance therapy (0.125-0.5 milligram, see next paragraph) without a loading dose results in development of steady-state plateau concentrations in about 7 days in patients with normal renal function.

The average daily oral maintenance dose is 0.125-0.5 milligram, usually 0.25 milligram. In the elderly patient, 0.125-0.25 milligram should be considered the average maintenance dose.

In patients with renal impairment, digoxin excretion is impaired and serum half-life is prolonged. Digitalizing and maintenance doses are lower than those recommended for patients with normal renal functions. Signs of digoxin toxicity develop sooner in patients with renal impairment, and it takes longer for toxic signs and symptoms to disappear. Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state plateau in patients with renal impairment than in patients with normal renal function.

It cannot be overemphasized that the values given are averages and substantial individual variation can be expected.

Children: Digitalization must be individualized. Generally, premature and immature infants are particularly sensitive, requiring reduced dosage that must be determined by careful titration.

Oral Dosage. Beyond the immediate newborn period, children require proportionally greater doses than adults on the basis of body weight or surface area. The recommended oral digitalizing dosages in children with normal renal function are:

Newborn infants (normal), up to 1 month, require 40-60 micrograms (mcg)/kilogram.
Infants, 1 month to 2 years, require approximately 60-80 micrograms (mcg)/kilogram.
Children, 2 years to 10 years, require 40-60 micrograms (mcg)/kilogram.
Children, over 10 years of age, require adult dosages in proportion to their body weight.
Maintenance therapy is 20-30 percent of the digitalizing dose administered each day.

Long term use of digoxin is indicated in almost all infants who have been digitalized for acute congestive heart failure unless the cause is transient. Many favor maintaining digoxin until at least 2 years of age in all infants with paroxysmal atrial tachycardia or in those who show either definite or latent failure.

Many children with severe inoperable congenital defects need digoxin throughout childhood and often for life.

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CLINICAL STUDIES

Altered Adrenergic Activity in Coronary Arterial Spasm: Insight Into Mechanism Based on Study of Coronary Hemodynamics and the Electrocardiogram

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To elucidate the pathophysiologic mechanism of coronary arterial spasm, the hypothesis was examined that underlying alterations in sympathetic activity may account for this syndrome in some patients. Observations were directed to alterations in coronary arterial hemodynamics and the electrocardiogram. Spasm of the left anterior descending coronary artery produced a mean increase in coronary vascular resistance of 107 percent ($P < 0.05$) in four patients in whom coronary sinus blood flow was measured with the thermodilution technique. The alpha adrenergic blocking agent phentolamine, given intravenously, acutely reversed coronary spasm and its clinical manifestations in eight patients and reduced coronary resistance. In four patients, administration of the long-acting oral alpha blocking agent phenoxybenzamine (20 to 80 mg/day) caused disappearance of symptoms during a follow-up period of 3 to 12 months. Transient prolongation of the corrected Q-T interval preceded spontaneous or ergonovine maleate-provoked coronary spasm in 11 patients with variant angina pectoris, whereas no significant change in the Q-T interval followed ergonovine administration in 27 control patients with atypical chest pain who did not have coronary spasm. T wave inversions in the resting electrocardiogram were normalized by isoproterenol infusion in one patient and by long-term phenoxybenzamine treatment in four patients with variant angina pectoris. These Q-T and T wave changes are analogous to those described with unilateral or asymmetric stellate ganglion stimulation in animals.

These observations suggest that alterations in the sympathetic nervous system that are consistent with asymmetric stellate ganglion activity and transient alpha adrenergic receptor stimulation can presage the development of coronary arterial spasm in some patients with variant angina pectoris.

From the Division of Cardiology and Department of Radiology, Stanford University School of Medicine, Stanford, California. This study was supported in part by Grant HL 5866 from the National Institutes of Health, Bethesda, Maryland. Dr. Ricci was supported by the Canadian Heart Foundation. Manuscript received August 15, 1978; revised manuscript received January 24, 1979, accepted January 24, 1979.

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Coronary arterial spasm has been established as a cause of Prinzmetal's variant angina[1,2] both in patients with normal coronary arteries and in those with obstructive coronary arterial lesions.[3–15] The pathophysiology of coronary spasm, that is, the mechanism whereby "temporarily in-

creased tonus"[1] occurs, must be identified if an effective approach is to be made to the management of patients with Prinzmetal's variant angina.

Hypotheses to explain coronary spasm include a local abnormality of vascular smooth muscle, possibly at the site of an obstructive lesion, a generalized disorder of metabolic or neural control mechanisms of the coronary circulation, or a combination of these factors. The autonomic nervous system has received considerable attention in discussions of the mechanism of coronary spasm.[11,12,16] Our purpose in this report is to summarize the information implicating the autonomic nervous system in coronary spasm, to present data that reflect the influence of the autonomic nervous system on the heart, and to propose the unifying hypothesis that alterations of the sympathetic nervous system can presage the occurrence of coronary spasm in some patients with variant angina pectoris and may be one pathophysiologic mechanism responsible for the abnormality in coronary blood flow.

Methods

Patients and procedures: We studied prospectively eight patients who had clinical features of Prinzmetal's variant angina pectoris. All had left heart catheterization with ventriculography and coronary arteriography by the Judkins technique. In five of these patients, we obtained reliable measurements of coronary sinus blood flow, which primarily reflects flow from the left coronary system,[17] using the thermodilution technique of Ganz et al.[18] The catheter (Wilton Webster Laboratories, Altadena, Calif.) was inserted deep into the coronary sinus from a left antecubital vein, and precautions were taken to ensure a stable catheter position within the sinus throughout the procedure.[19] Although this technique does not permit a valid assessment of absolute flow per unit weight of myocardium, and cannot measure regional redistribution of flow, it is suitable for measuring the direction and magnitude of an acute change in flow in an individual patient. In our laboratory, repeat measurements of coronary sinus flow agree to within 4 percent.[20] Coronary vascular resistance was calculated by the quotient of mean arterial pressure (determined from the direct intraarterial pressure tracing as 1/3 [systolic + 2× diastolic])[21] and coronary sinus flow.

Provocation and reversal of coronary spasm: At the time of study, each patient was experiencing multiple episodes of chest pain each day, many of these occurring in the early morning hours. No attempt was made to alter the basic treatment regimen, except that propranolol was discontinued at least 12 hours before study. To six patients who did not have chest pain spontaneously during coronary arteriography, and whose coronary arterial anatomy did not appear to explain the clinical features, we administered ergonovine maleate intravenously in three doses of 0.05, 0.1 and 0.25 mg sequentially at 3 minute intervals and monitored blood pressure and 12 lead electrocardiograms continuously. When chest pain occurred, we recorded the electrocardiogram and visualized the coronary artery corresponding to the electrocardiographic S-T segment changes. Immediately thereafter, each patient received phentolamine mesylate, 10 mg intravenously, and electrocardiography and selective arteriography were repeated within 2 minutes. Each patient gave informed consent for coronary sinus blood flow measurement and ergonovine administration in accordance with the requirements of the Stanford University Medical Committee on the Use of Human Subjects in Research. No major complications occurred during the procedures.

Electrographic recordings: Suitable electrocardiograms recorded at 25 mm/sec or 50 mm/sec were available for measurement of Q-T intervals[22] before spontaneous or ergonovine-induced spasm in seven of these eight patients, in four additional patients who had spasm documented angiographically after ergonovine administration and in 27 control patients with atypical chest pain and normal coronary arteries in whom pain, S-T segment changes or coronary spasm could not be provoked by ergonovine. Although two patients had recurrent serious ventricular arrhythmias during spasm, no patient was receiving antiarrhythmic agents or other drugs known to alter the Q-T interval at the time of study. Electrocardiograms recorded during chest pain, spasm, coronary injection or in the presence of S-T segment changes suggestive of ischemia were excluded. At least three successive Q-T intervals were meausred[22] from lead II or V_5 in each patient, and the mean Q-T interval was corrected for heart rate and expressed as corrected Q-Tc interval (Q-Tc), where Q-Tc = the

TABLE I

Clinical Features at Rest and During Spasm in Eight Patients Studied Prospectively

Case no.	Age (yr) & Sex	Duration of Symptoms (yr)	Electrocardiogram At Rest	Electrocardiogram With Pain	Stenosis in Control Angio	Location and Magnitude of Spasm	ΔCVR During Spasm
1	45M	2	T↓ V_4–V_6	ST↑ V_1–V_3	80% LAD	LAD 99%, spont	0.22
2	55F	2	T↓ V_2–V_4	ST↑ V_1–V_6	70% LAD	LAD 99%, erg	0.34
3	40F	1	T↓ V_2–V_5	ST↑ II, III, aVF	80% dist RCA	LAD 50%, RCA 100% } erg	
4	40M	3	NI	ST↑ II, III, aVF	NI	RCA 40% spont	
5	50M	3	T↓ V_2–V_6	ST↑ V_1–V_6	30% LAD	LAD 100% erg	1.27
6	49F	1	NI	ST↑ V_1–V_6	NI	LCx 70%, RCA 70%, LAD 99% } erg	1.64
7	39M	1/2	NI	ST↓, T↓ II, III, aVF	20% RCA	RCA 70% erg	−0.08
8	58M	1/3	NI	ST↑ V_2–V_4	50% LAD	LAD 100%, erg	

Angio = coronary angiogram; CVR = coronary vascular resistance (mm Hg/ml per min); dist = distal; erg = ergonovine maleate; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; NI = normal; RCA = right coronary artery; spont = spontaneous; Δ = change; ↓ = depressed; ↑ = elevated.

Q-T interval divided by the square root of the R-R interval ($Q\text{-}T/\sqrt{R\text{-}R}$).

Results

Clinical and angiographic features: Table I summarizes the clinical features and results of angiography for the eight patients studied prospectively. Chest pain was most frequent during the early morning hours in all patients, and often woke the patients. Sublingual nitroglycerin always provided prompt relief; however, two patients required 80 to 100 tablets/week, and another patient experienced intolerable flushing. No patient had effort-related angina. Resting electrocardiograms showed T wave inversion in four patients. S-T segment elevation occurred in all patients during pain, although in one patient pain was occasionally accompanied by S-T depression. This variability of S-T segment response during spasm is now well established.[23] The electrocardiographic changes were in leads corresponding to the area supplied by the vessels in which spasm developed. The explanation for S-T elevation occurring subsequent to vessel narrowing of only 40 percent during spasm in Patient 4 (Table I) is not readily apparent. Possibilities are that the degree of narrowing was underestimated by visualization of the artery in a single obliquity, or that spasm of arterioles (or resistance vessels)[24] was coexistent. The S-T depression that occurred during a reduction in vessel diameter of 70 percent (Patient 7) is consistent with subtotal occlusion and nontransmural ischemia. Malignant ventricular arrhythmias were not a feature of the clinical syndrome in any of these eight patients.

All patients had normal left ventricular end diastolic pressure at rest and none had segmental contraction abnormalities on ventriculography. Coronary arteriography showed normal vessels in two patients, fixed luminal obstruction of 50 percent or less in three patients and obstruction greater than 50 percent in three patients.

Coronary arterial spasm: release by alpha adrenergic blockade: The changes in coronary hemodynamics during coronary spasm in Patient 5 have been presented in detail previously.[20] Figure 1 shows representative frames from the angiograms taken during the control state, at the peak of spasm and after release of spasm by phentolamine in Patients 1 and 2. In the six patients given ergonovine maleate, spasm occurred after 0.05 mg in one, after 0.15 mg in one and after a total of 0.4 mg in four, and in all reproduced the clinical syndrome. Heart rate changed insignificantly from 75 ± 5 beats/min (mean ± standard error of the mean) in the control period to 77 ± 4 beats/min during coronary spasm; the mean arterial pressure increased from 98 ± 7 to 108 ± 8 mm Hg ($P < 0.0025$). Changes in heart rate and blood pressure were similar for both spontaneous and ergonovine-provoked spasm. In the patients with spasm of the left coronary system, the mean coronary vascular resistance increased 107 percent from 0.74 ± 0.13 to 1.61 ± 0.46 mm Hg/ml per min ($P < 0.05$). In most instances, pain and S-T elevation preceded in-

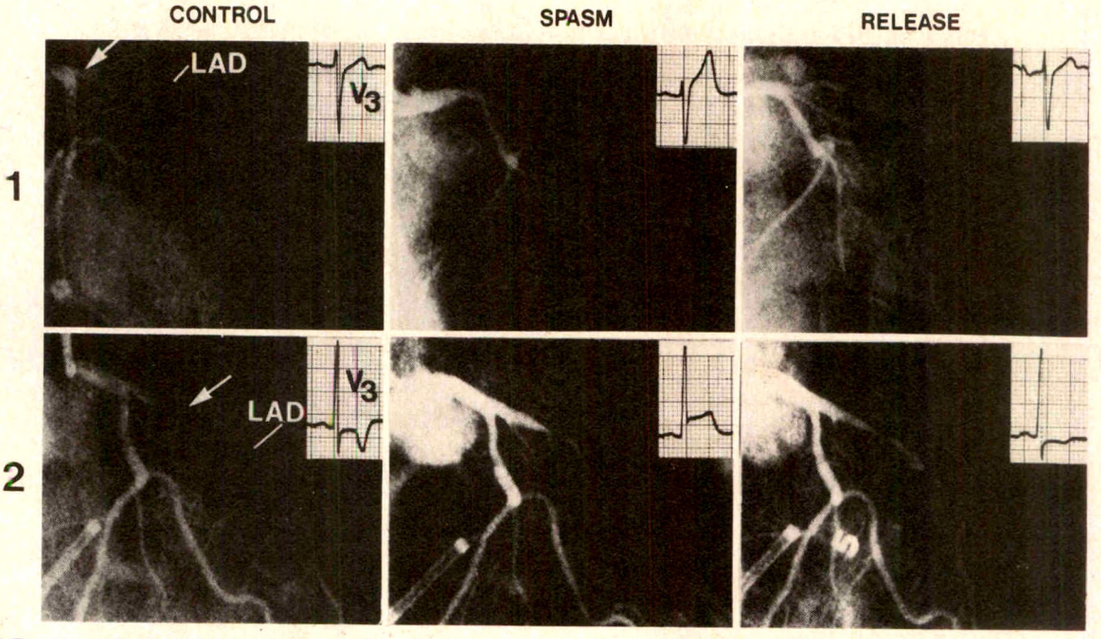


FIGURE 1. Representative frames from the coronary angiograms of Patients 1 and 2 during the control state and coronary spasm and after phentolamine-induced release of spasm. The electrocardiogram recorded just before each injection is in the inset. **Arrows** indicate the site of fixed coronary narrowing. The catheter seen in some views is the thermodilution coronary sinus catheter. In Patient 1, complete occlusion occurred during spontaneous spasm at the site of an 80 percent obstructive lesion in the left anterior descending coronary artery (LAD), accompanied by S-T segment elevation in lead V_1 to V_3. In Patient 2, ergonovine-provoked spasm of the left anterior descending coronary artery occurred distal to a 70 percent narrowing, accompanied by S-T elevation in lead V_3. In both cases, phentolamine caused complete relief of spasm and return of the S-T segment to the baseline value.

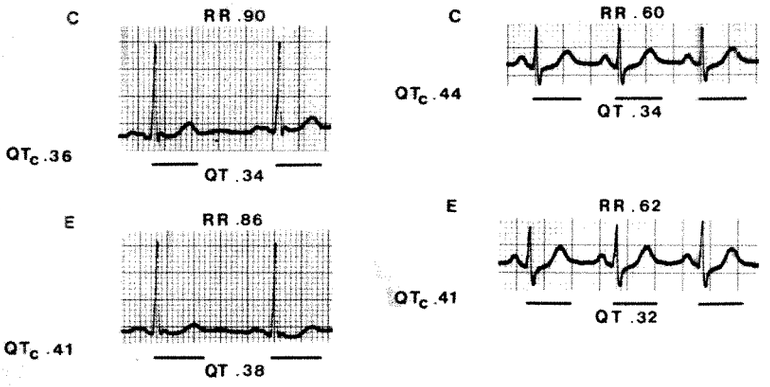


FIGURE 2. Representative electrocardiographic strips recorded at 25 mm/sec and enlarged before (C = control) and after ergonovine (E) administration in a patient who subsequently had coronary spasm (**left panels**) and in a patient with atypical chest pain (**right panels**). The R-R interval (second) is above each tracing. The measured Q-T interval (with the duration delineated by the **solid horizontal line**) is below each recording; the corrected Q-T interval ($Q\text{-}T_c$ = Q-T measured/$\sqrt{\text{R-R}}$) is to the left.

sertion of the catheter into the coronary ostium. When spasm occurred while the catheter remained in place, it occurred distal to the catheter tip, was accompanied by pain and S-T segment changes and caused marked narrowing or disappearance of distal vessels. These features have not accompanied catheter-induced spasm in our laboratory or in those of others.[25,26]

Phentolamine administration, 10 mg intravenously, caused disappearance of the coronary spasm, S-T abnormality and angina in less than 2 minutes in seven of eight patients (Fig. 1C), and a reduction in the coronary vascular resistance in the three patients in whom coronary sinus flow measurements were repeated. In Patient 6, who had the most intense spasm of the group, with coronary resistance increasing threefold from 0.81 to 2.45 mm Hg/ml per min, the first dose of phentolamine did not reverse spasm. Pain was reversed shortly after simultaneous administration of nitroglycerin, 0.6 mg sublingually, and a repeat dose of phentolamine intravenously. This patient had responded quickly and completely to phentolamine given during prior episodes of spontaneous spasm and during a previous episode of ergonovine-induced spasm. A more intense degree of spasm may have been responsible for the apparent unresponsiveness of phentolamine on one occasion in this patient, and may have necessitated a larger initial dose.

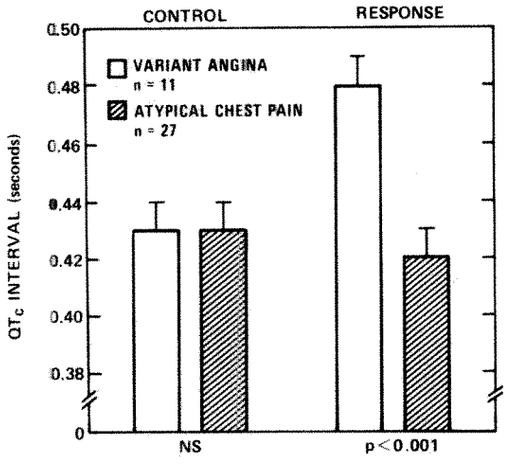


FIGURE 3. $Q\text{-}T_c$ interval during the control state (**left**), and just before spontaneous or ergonovine-provoked spasm (**right**) in 11 patients with variant angina pectoris (**clear bars**) and before and after ergonovine maleate in 27 patients with atypical chest pain (**hatched bars**) who did not have coronary spasm. In the former group, a significant lengthening of the $Q\text{-}T_c$ interval preceded coronary spasm; in the latter group, $Q\text{-}T_c$ interval shortening occurred after ergonovine administration. The difference in response between the groups is significant ($P < 0.001$). n = number of patients; NS = not significant; p = probability.

Q-T interval: Figure 2 illustrates typical changes in the Q-T interval in a patient from each group. Figure 3 shows the results of the change in Q-T interval corrected for heart rate ($Q\text{-}T_c$) measured in 11 patients with variant angina pectoris and 27 patients with atypical chest pain. The mean basal $Q\text{-}T_c$ interval for both groups was the same, 0.43 ± 0.01 second. In patients who had no coronary spasm, the mean $Q\text{-}T_c$ interval shortened 0.01 ± 0.01 second after ergonovine administration ($P < 0.025$) compared with a $Q\text{-}T_c$ prolongation of 0.05 ± 0.01 second ($P < 0.001$) just before spontaneous or ergonovine-provoked spasm in patients with variant angina. The difference in response between the groups was highly significant ($P < 0.001$ by Student's *t* test for unpaired data).

Discussion

Alpha adrenergic mediation of coronary spasm: Coronary resistance is influenced in the resting state by the alpha adrenergic nervous system.[27] In patients with fixed atherosclerotic coronary arterial narrowing, alpha adrenergically mediated increases in coronary resistance may be a factor in the pathogenesis of angina.[28] Our findings that alpha adrenergic blocking agents can reverse coronary spasm suggest that a pathologic alteration of the alpha adrenergic system may be the mechanism for spasm in some patients with variant angina pectoris. Alpha adrenergic mediation of coronary spasm is not a new idea. Yasue et al.[11,16] proposed that stimulation of alpha receptors mediated the spasm provoked by subcutaneous injection of epinephrine after beta adrenergic blockade. In one patient, treatment with phenoxybenzamine suppressed attacks of variant an-

gina.[16] Endo et al.[12] showed that methacholine injection could precipitate coronary spasm in three patients with variant angina, and Yasue et al.[16] proposed that methacholine stimulated the preganglionic cholinergic sympathetic fibers to excite alpha adrenergic receptors acting upon the coronary arteries. Levene and Freeman[13] used phentolamine to reverse spasm during coronary arteriography and have reported improvement in clinical symptoms in their patient treated with phenoxybenzamine.

Mechanism of phentolamine action and therapeutic application: In our study, phentolamine caused relief of chest pain, reduction in coronary vascular resistance, reversal of coronary spasm and a return of the electrocardiogram to the control state. The possibility that phentolamine may have acted by blocking the effects of increased circulating catecholamines or by direct smooth muscle dilation, an effect shown to be prominent in peripheral circulation,[29] cannot be excluded. However, we have recently shown that these effects account for less than one quarter of the action of phentolamine upon coronary vascular resistance in man[27] and therefore are not likely to have played a dominant role in this study.

Because marked reversal of the coronary hemodynamic effects of spasm by phentolamine suggested an effective antiadrenergic action, we administered the long-acting oral alpha blocking agent, phenoxybenzamine, to four patients. (Cases 1, 2, 3 and 5) whose use of nitrates was excessive or poorly tolerated. Starting at daily doses of 10 mg, and reaching levels of 20 to 80 mg/day over a period of 2 to 4 weeks, phenoxybenzamine administration was associated with complete disappearance or a marked reduction in frequency of chest pain, judged by a reduction in nitroglycerin requirement to less than five tablets per week, during a follow-up period of 3 to 12 months. Malaise accompanied the initial therapy in three patients, and its persistence necessitated discontinuing therapy in one of these patients. Orthostatic symptoms occurred with therapy, but have been tolerable in all cases. Although limited, this experience illustrates that alpha adrenergic blockade may be effective in preventing recurrent coronary spasm in some patients resistant to, suffering side effects of or requiring excessive use of nitrate therapy. A carefully controlled study will be necessary to confirm this observation. Nevertheless, the effectiveness of both acutely and chronically administered alpha adrenergic blocking agents in reversing and preventing spasm suggests that an alpha adrenergically mediated mechanism is operative in the pathogenesis of coronary spasm.

Ergot alkaloids, including ergonovine, have been shown to produce effects by excitation of adrenergic receptors[30,31] and some produce changes by a centrally mediated autonomic action.[32] Ergonovine, given to patients who do not have coronary spasm, is associated with no significant changes in coronary vascular resistance in spite of an increase in cardiac demand, suggesting an effect on arteriolar resistance vessels.[33]

Q-T prolongation as a marker presaging coronary spasm: Consistent lengthening of the Q-T_c interval just prior to the occurrence of spasm-induced ischemia suggests that this may be a marker for events presaging coronary spasm. We cannot explain the discrepancy of our data with those of Curry et al.,[34] who showed no significant change in the Q-T_c interval during ergonovine-induced spasm. Recent evidence implicates the autonomic nervous system in producing changes in the Q-T interval and also in the polarity of the T wave. Yanowitz et al.[35] showed that unilateral stellate ganglion stimulation or stellate ganglionectomy could produce T wave inversion or Q-T interval prolongation in dogs. Because these electrocardiographic changes are similar to those seen in patients with central nervous system disease, the authors hypothesized that a unilateral alteration of sympathetic tone, possibly at the hypothalamic level, may explain them. The possibility that Q-T_c prolongation in our patients represents occult or early ischemia is unlikely because S-T segment shifts are characteristically the earliest electrocardiographic manifestations of ischemia.[36] Q-T prolongation occurs either as a late phenomenon after the onset of ischemia, or not at all.[37,38] Even though regional wall motion disturbances occur within a few beats after acute coronary occlusion,[39] any resultant local redistribution of blood flow does not produce repolarization abnormalities such as Q-T interval alterations in the conscious dog until after S-T segment shifts are well established (Kumada T, Ricci DR, Ross J Jr, unpublished observations).

T wave inversions in coronary spasm versus "neurogenic" T waves: Daoud et al.[40] showed that isoproterenol infusion normalized the T wave inversions in all patients with central nervous system disease but did not do so in patients with T wave abnormalities attributed to ischemia or pericarditis. Kuo and Surawicz[41] recently extended that observation, showing that, in dogs, changes in T wave polarity produced by right stellate stimulation or left stellate ganglionectomy are reversed by isoproterenol infusion.

The T wave inversions noted in the resting electrocardiogram in four of our patients (Table I) were reminiscent of "neurogenic" T waves. After therapy with phenoxybenzamine had resulted in relief of symptoms in these patients, the T waves returned to normal. Before phenoxybenzamine was administered to Patient 5, an infusion of isoproterenol, 0.75 μg/min, caused prompt normalization of his T waves (Fig. 4). After 3 weeks of therapy with phenoxybenzamine, coincident with marked reduction in the frequency of variant angina, his T wave inversions normalized. A similar effect on resting T wave inversion in response to isoproterenol infusion has been observed by one of us (A. E. O.) in a patient with variant angina and normal coronary arteries. Although an ischemic etiology for the T wave inversions is possible, no other signs or symptoms of ischemia were manifest in the basal state; there was absence of chest pain and S-T segment abnormalities, and the left ventriculogram was normal. T wave inver-

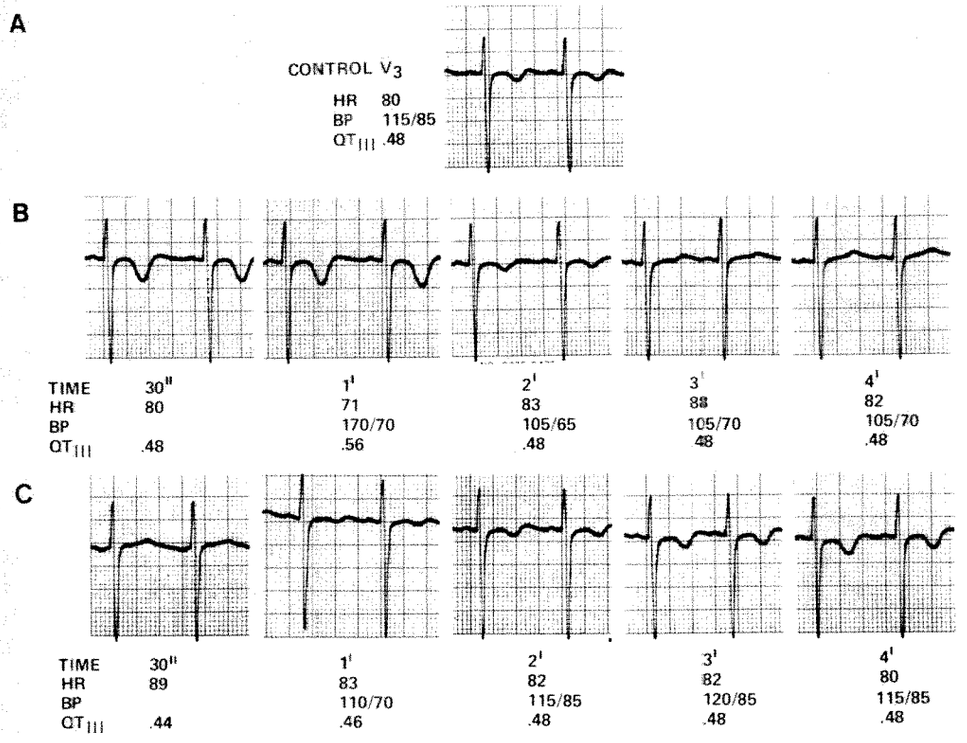


FIGURE 4. Patient 5. Representative lead V_3 tracings at control (**A**), during 4 minutes of isoproterenol infusion (0.75 μg/min) (**B**) and for 4 minutes after discontinuation of the infusion (**C**). Also shown are the heart rate (HR) in beats/min, blood pressure (BP) in mm Hg (indirect brachial arterial pressure measured with a mercury sphygmomanometer) and Q-T interval in seconds measured from lead III (QT_{III}). After a slight deeper inversion of the T wave initially, the polarity gradually reversed during isoproterenol infusion and returned to the baseline configuration within 4 minutes after the infusion was discontinued.

sions on the resting electrocardiogram of patients with variant angina have been widely reported[6,7,10,11,42–45] and are usually described as "nonspecific" or ischemic T wave abnormalities. The response to isoproterenol infusion in our patient (Fig. 4) would not be expected in a patient with ischemia,[40] but would be compatible with a "neurogenic" etiology as proposed by Yanowitz[35] and by Kuo and Surawicz.[41]

T wave changes and asymmetric adrenergic excitation: Normalization of the inverted T waves in our patients also occurred in association with chronic alpha blockade with phenoxybenzamine and was coincident with improvement of their symptoms. These data and the prolongation of the Q-T interval noted to occur before signs or symptoms of ischemia occurred in response to spontaneous or ergonovine maleate-provoked spasm appear to be clinically analogous to the effects of unilateral or asymmetric stellate ganglion activity produced in experimental models.[35,41,46] In the experimental studies, changes in the surface electrocardiogram may be explained by alterations in the monophasic action potentials on the anterior wall of the ventricle (compared with the posterior wall) produced by asymmetric adrenergic excitation, whereas isoproterenol produces unequal changes of the monophasic action potential on the anterior and posterior walls, restoring the normal relation between their durations.[41,46] Alpha adrenergic blockade may produce effects on the monophasic action potentials by antagonizing the adrenergic neurotransmitter, norepinephrine, thereby canceling a state of unilateral overactivity. The absence of T wave inversion in the resting electrocardiogram does not exclude unilateral adrenergic overactivity, because during some circumstances of unilateral stellate stimulation or ganglionectomy no change occurs in the T wave or a small change occurs in the same direction as its baseline polarity.[35]

Proposed mechanism of coronary spasm in some patients with variant angina pectoris: Because of a functional abnormality in the autonomic nervous system, possibly at a hypothalamic level, a state of adrenergic imbalance exists so that, at rest, the right or left stellate ganglion modulates enhanced nerve traffic, producing T wave abnormalities. In this imbalanced state, bursts of sympathomimetic activity, which may occur spontaneously or provocably by epinephrine, methacholine or ergonovine, may result in inordinate excitation of a stellate ganglion, producing Q-T interval prolongation. Transmission of activity along one or more of its cardiac branches[47] causes selective coronary spasm accompanied by a marked increase in coronary resistance. Alpha adrenergic blockade, by antagonizing the sympathetic neurotransmitter, norepinephrine, cancels the effect of asymmetric stellate ganglion activity. Measurement of coronary sinus and systemic catecholamine concentration and direct measurement of cardiac nerve activity during coronary spasm would be necessary to confirm this mechanism.

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Variant Angina Pectoris: Investigation of Indexes of Sympathetic Nervous System Function

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One thousand forty-five spontaneous episodes of S-T segment elevation were observed in three patients over a total of 72 days of continuous electrocardiographic monitoring. Eighty-nine percent of episodes were asymptomatic; chest pain tended to occur with episodes longer than 3 minutes, and ventricular ectopy occurred almost exclusively with symptomatic episodes. Nitroglycerin regularly relieved angina or S-T elevation, or both.

Plasma and urinary catecholamines and their metabolites were normal. Episodes of variant angina were not associated with a generalized increase in sympathetic outflow because serum catecholamine levels at the onset and termination of the S-T abnormalities were not elevated. Controlled trials of propranolol showed no significant beneficial effect. Propranolol significantly increased the length of episodes of S-T elevation in one patient, increasing ventricular irritability. The overall course of variant angina was quite variable, with spontaneous and long-lasting remissions, necessitating cautious interpretation of clinical trials.

The concept of coronary vasospasm as a cause of angina pectoris received little attention until Prinzmetal et al.[1,2] hypothesized that "a temporary and often cyclic increase in tonus in a narrowed vessel" [2] might be responsible for episodes of ischemic cardiac pain and S-T segment elevation. With angiographic documentation of spasm during spontaneous episodes of angina,[3,4] the syndrome of vasospastic angina is now well established.[5] Demonstration of reversible vasospasm in a significant proportion of unselected patients at the time of myocardial infarction[6] and before infarction[7] extends the previous observations to include myocardial necrosis as a possible consequence of spasm and lends impetus to inquiries into the cause and therapy of variant angina.

Although many possible causes for this syndrome have been proposed,[8] the multiple physiologic and pharmacologic stimuli reported to induce attacks[9–16] suggest that underlying autonomic dysfunction[12] may be a cause. Because the origin of vasospastic angina is still uncertain, many therapeutic agents have been tried and have been reported to be beneficial; however, there have been few carefully conducted controlled trials because quantitation of benefit has depended on symptomatic relief or intermittent electrocardiographic recordings. We therefore investigated humoral and hemodynamic indexes of autonomic nervous system function in three patients with frequent variant angina. We then used continuous electrocardiographic recordings to quantitate their episodes of S-T elevation, allowing objective documentation of results of a controlled single blind crossover trial of propranolol.

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Methods

Electrocardiographic monitoring procedures: Three patients with variant angina were studied. All had had S-T elevation documented at rest without changes in blood pressure or heart rate, and all had undergone angiography, stress testing, echocardiography and a trial of conventional antianginal therapy. After giving informed consent, they were admitted to the Elliott V. Newman Clinical Research Center of Vanderbilt University, where they underwent constant ambulatory electrocardiographic recordings for the duration of the studies. A monitor lead was chosen to correspond to the lead in which S-T elevation was maximal, using the 12 lead electrocardiogram as reference. A Hewlett-Packard model 78100A telemetry system transmitted electrocardiographic signals to the hospital coronary care unit and also to an Ampex model FR 1200 tape recorder. Tapes were reviewed using an oscilloscopic display of superimposed successive electrocardiographic complexes at 32 times real time and an interactive computer program developed in the Biomedical Engineering Division of Vanderbilt University that allowed tabulation of all episodes of S-T segment shift and their duration. Selected segments of electrocardiographic tape were recorded as contourograms using an adaptation of the technique of Riggins et al.[17] (Fig. 1).

Autonomic nervous system monitoring: *Provocative stimuli attempted in each patient included* (1) carotid massage, (2) gag reflex, (3) rectal tone examination, (4) ice-water drinking, (5) hyperventilation, (6) cigarette smoking, and (7) the Valsalva maneuver.

Tests of sympathetic functional integrity (*Table I*) *included* (1) the venous reflex,[18] (2) treadmill testing, (3) cold pressor test, (4) isometric handgrip test, (5) orthostasis and a Valsalva maneuver performed during echocardiography.[19] These tests were performed in quiet surroundings to eliminate external stimuli. The venous reflex values were each the average of two trials with deep inspiration and two with the Valsalva maneuver. The treadmill catecholamine levels were drawn at the end of 1,386 kilogram-meters (kg-m) of work done in 3 minutes, and blood for these samples was drawn through an indwelling needle to eliminate the effect of venipuncture. The Valsalva maneuver, performed separately from that used for the venous reflex test, was 40 torr pressure held for 20 seconds, accomplished by blowing into a mouthpiece connected to a manometer. The cold pressor test measured the increase in mean blood pressure after 3 minutes of immersion of one hand in ice water; for isometric handgrip, the patient maintained 30 percent of his maximal grip for 3 minutes. The left atrial dimension during the Valsalva maneuver decreases by 18 to 66 percent in normal subjects, but this response is diminished in conditions of heightened sympathetic activity such as congestive heart failure.

Biochemical assessment of sympathetic function (*Table II*) *included* measurement of plasma norepinephrine, epinephrine and dopamine in addition to urinary catecholamines, metanephrine, normetanephrine and vanillylmandelic acid. Because changes in sodium balance may alter sympathetic nervous system activity,[20] patients were maintained on a constant sodium diet of 150 mEq/day. Catecholamines were monitored at rest, after certain sympathetic stimuli and during two episodes of S-T segment elevation. Plasma for supine determinations was drawn at 8:00 A.M. through an indwelling scalp-vein needle placed at 7:30 A.M., the patient

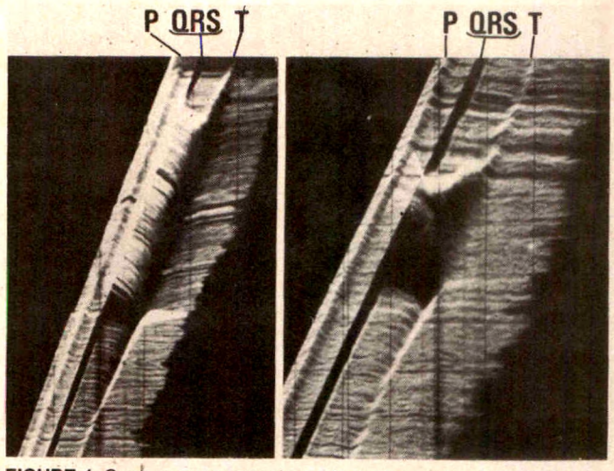


FIGURE 1. Contourograms produced from the continuous electrocardiographic recordings before, during and after episodes of typical variant angina in Patient 1 (**left**) and Patient 2 (**right**). Each P-QRS-T segment is aligned beginning at the P wave and shifted slightly to the left of the previous segment. A vertical oscilloscopic sweep represents 10 minutes real-time. The QRS complex is seen as a dark space because of its rapid motion perpendicular to the plane of the tracing. The S-T segment at the beginning of each contourogram is seen to be isoelectric with the P-R segment; with the episode of variant angina, there is a slight change in T wave configuration, followed by a dramatic rise in the S-T segment and deep T wave inversion. The rapid spontaneous return of the S-T segment to the baseline level and the slightly longer persistence of the T wave abnormality are easily appreciated.

TABLE I

Sympathetic Function Tests

	Patient 1	Patient 2	Patient 3	Normal Values
1. Venous reflex (torr)	22	36	12	5–35
2. Treadmill-induced level (pg/ml) of				
Norepinephrine	1225	947	1064	500–1500
Epinephrine	81	20	68	50–250
Dopamine	14	62	42	<100
3. Valsalva maneuver (beats/min)*	98/54	110/60	92/76	90–120/50–70
4. Cold pressor test (torr)†	+18	+26	+20	12–30
5. Isometric handgrip test (torr)†	+15	+26	+38	15–40
6. Left atrial size during Valsalva maneuver (%‡)	−18	−29	−24	18–66

* Maximal heart rate during strain phase/minimal heart rate during overshoot phase.
† Increase in mean blood pressure.
‡ Reduction in diameter measured in the one dimensional echocardiogram.

having been supine from midnight until 8:00 A.M. That for upright determinations was drawn through the same needle after patients had been ambulatory and upright for 3 hours. In patients 1 and 3, plasma was drawn after S-T elevation was noted on the monitor but before pain began, and again just after the S-T segment had returned to baseline.

Urinary levels of 5-hydroxyindoleacetic acid were measured and plasma renin activity, free thyroxine and levels of 2,3-diphosphoglycerate were assessed. In addition, hemoglobin-oxygen affinity was determined, and creatine kinase levels after prolonged episodes of angina were measured.

The simultaneous differential assay of norepinephrine, epinephrine and dopamine by a radioenzymatic method has been described.[21] This assay is sensitive to 20 pg/ml of plasma for norepinephrine and epinephrine and 30 pg/ml of plasma for dopamine. Metanephrine and normetanephrine were measured using a mass spectrometric method recently described.[22]

Propranolol trial: Administration of propranolol was begun (using a single blind procedure in one subject, a double blind procedure in two subjects) after a 3 day trial of placebo and was given at a dose of 160 mg four times daily for 3 days. In Patient 1, an interim trial of 40 mg four times daily was interposed between the placebo and full dose regimens. After the discontinuation of propranolol, monitoring continued while the patient was receiving placebo. Intermittent short-acting nitrates were used to treat symptomatic episodes of S-T elevation during both the propranolol and placebo periods, but all other drugs were stopped.

Patients: Two men and one woman, aged 62, 57, 47 years, respectively, had had nonexertional episodes of typical ischemic cardiac pain for 5, 2 and 6 years, respectively, with Patients 1 and 3 having multiple periods of weeks to months free of pain, alternating with symptomatic periods that required occasional hospitalization. The electrocardiogram was normal in Patients 1 and 2 but showed minor, nonspecific ST-T wave abnormalities in Patient 3. Coronary arteriography in all patients showed narrowing of less than 40 percent of arterial diameter in the right coronary artery in Patients 1 and 2 and in the proximal left anterior descending coronary artery in Patient 3. In Patient 3 a single bypass graft to the left anterior descending artery had been placed 3 years before our study, and postoperative angiography showed total occlusion of this artery but a widely patent graft. There had been no change in the patient's symptoms. In all patients, episodic S-T elevation was seen in leads appropriate to the coronary arterial segment with mild narrowing. Physical examination was normal in all three patients, and Patients 1 and 2 had had prior normal evaluations of the gastrointestinal system.

Results

Provocative maneuvers: Carotid massage, gag reflex, rectal tone examination, icewater drinking, hyperventilation, cigarette smoking, the Valsalva maneuver and treadmill testing have all been reported to induce attacks in some patients with variant angina. Our patients did not respond to any of these maneuvers except the gag reflex and hyperventilation, and only Patient 3 responded even occasionally to these. The treadmill test in Patient 3 was inadequate because it was prematurely terminated because the patient was "tired all over" at a heart rate of 125 beats/min (target rate 149 beats/min) without electrocardiographic changes or decrease in blood pressure.

Tests of sympathetic function (Table I): The venous reflex, a measure of sympathetic outflow to hand veins as reflected in altered venous tone, was not generally suggestive of excessive sympathetic function. The venous responses in Patients 1 and 3 were well within the normal range, but Patient 2 had the largest stimulated increase in tone we have observed. Because of the technical variability of this test and the lack of a well standardized upper limit of normal, cautious interpretation of this result is required. Fortuitously, while baseline venous tone was being monitored in Patient 1 before introduction of the sympathetic stimulus, a spontaneous episode of S-T elevation occurred. No alteration in venous tone was seen during the first 3 minutes of the attack, although a slight increase in tone

TABLE II

Biochemical Indexes of Sympathetic Function

	Patient 1	Patient 2	Patient 3	Normal Values
1. Supine catecholamines (pg/ml)				
Plasma norepinephrine	184	211	164	150–300
Plasma epinephrine	42	10	36	50
Plasma dopamine	71	76	40	100
2. Upright catecholamines (pg/ml)				
Plasma norepinephrine	472	635	524	300–700
Plasma epinephrine	77	17	42	<50
Plasma dopamine	18	44	55	<100
3. At onset of S-T elevation (pg/ml)*				
Plasma norepinephrine	162	. . .	176	NA
Plasma epinephrine	33	. . .	20	NA
Plasma dopamine	48	. . .	54	NA
4. At end of S-T elevation (pg/ml)*				
Plasma norepinephrine	193	. . .	184	NA
Plasma epinephrine	44	. . .	38	NA
Plasma dopamine	46	. . .	42	NA
5. 24-hour urinary VMA (mg)	4.7	2.5	2.4	0.8–7.0
6. 24-hour urinary catecholamines (μg)	74	63	90	<106
7. 24-hour urinary normetanephrine (μg)	260	310	288	<800
8. 24-hour urinary metanephrine (μg)	168	124	154	<400

* Samples drawn with the patient supine.
NA = not applicable; VMA = vanillylmandelic acid; . . . = not measured.

was observed later, after the patient noted precordial distress. This increase was less than that induced by the Valsalva maneuver and deep inspiration.

The levels of norepinephrine, epinephrine and dopamine associated with a standardized treadmill test (4 miles/hour with grade adjusted so that 1,386 kg-m of work were accomplished in 3 minutes) were not significantly different from those observed in normal subjects.[23] Similarly, the hemodynamic responses to the cold pressor test, isometric handgrip test and the Valsalva maneuver were within the normal range. Although the change in left atrial size during the Valsalva maneuver was at the lower limit of normal, it was greater than the change usually seen even in mild heart failure.[19]

No elevation in creatine kinase levels was observed in any patient. Urinary 5-hydroxyindoleacetic acid, plasma free thyroxine levels and supine and upright plasma renin activity levels were all normal, as were hemoglobin-oxygen affinity and 2,3-diphosphoglycerate levels.

Biochemical indexes of sympathetic function: The results of plasma and urinary studies of catecholamines and their metabolites (Table II) were within the normal range. In two patients, it was possible by lengthy bedside monitoring to sample for plasma catecholamines at the onset of S-T elevation and again 5 minutes (Patient 3) and 8 minutes (Patient 1) later, at the moment of resolution of S-T elevation. Both of these episodes were associated with pain, and in both cases the pain appeared 3 minutes after the electrocardiographic changes were observed. Hence, the initial sample was taken when the patient was pain-free and the second while he was experiencing precordial distress. Plasma catecholamine values, both at the onset and at the end of S-T elevation, were lower than those associated with as mild a stimulus as upright posture.

Propranolol trial: All three subjects had been receiving outpatient treatment with propranolol, 40 mg orally four times daily, with little apparent benefit. Increasing the dosage to 160 mg orally every 6 hours appeared to be detrimental in Patient 1 (Fig. 2), resulting in longer episodes of S-T elevation and increased severity of ventricular arrhythmias, but it had no effect on the course of disease in the other patients. The same dosage was repeated in Patient 1 at a time when he was asymptomatic and monitoring showed only very brief episodes of S-T elevation (less than 2 minutes); the previously observed increase in length of episodes did not recur.

Nitrate therapy: If nitrate therapy was sufficient, patients could be maintained free of attacks. This usually required administration of 10 mg of sublingual isosorbide dinitrate every 2 hours, day and night. A regimen of nitroglycerin ointment, 1 to 2 inches (2.5 to 5 cm) every 6 hours, was partially successful in two patients; a regimen of treatment every 4 hours prevented attacks, but the associated headache was pronounced.

Course in hospital: During the 22 to 26 days of hospitalization entailed by these studies, each patient had frequent episodes of S-T elevation (569 episodes in Patient 1 and 284 and 192 episodes in Patients 2 and 3, respectively), most of which were brief (less than 4 minutes) and asymptomatic. This is best exemplified by Patient 1, who perceived only 11 percent of his episodes of S-T elevation. In this patient, the duration of S-T elevation ranged from 15 seconds to 11 1/4 minutes,

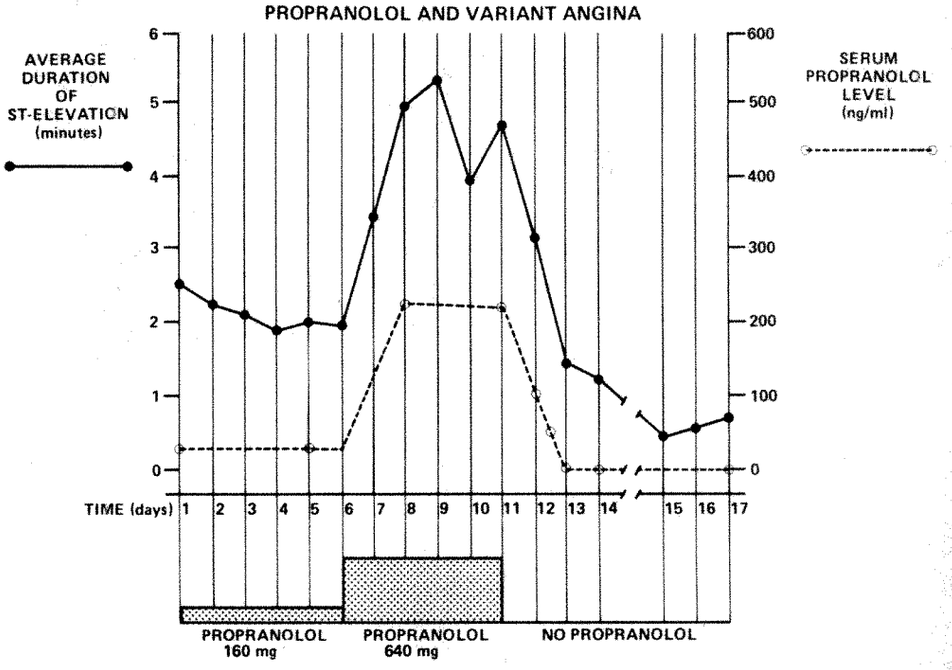


FIGURE 2. Patient 1. Effect of propranolol therapy. Note that the average duration of S-T elevation (minutes that each episode lasted) was greatest while the patient was receiving propranolol, 640 mg daily, less with the smaller dosage of propranolol and least while receiving no medication. Ventricular premature complexes, seen only with episodes of S-T elevation were more frequent with longer episodes, and bigeminy only occurred during large dose propranolol treatment. The number of episodes gradually decreased over the course of this trial (not plotted) and was not significantly related to the dosage of propranolol.

with 87 percent lasting less than 4 minutes. The longest asymptomatic episode was 8 minutes in length, but most episodes longer than 4 minutes were felt by the patient. Patients 1 and 3 had premature ventricular complexes that occurred in Patient 1 only with episodes of S-T elevation and were more frequent in both patients with longer episodes of S-T elevation.

All patients had gradual improvement during their hospital stay, with a spontaneous decrease in the frequency and length of episodes that appeared to be unrelated to the therapeutic agents used. Patients 1 and 2 were free of pain and S-T elevation without any medication at the time of discharge, and Patient 3 had less frequent episodes, though some did persist.

Discussion

Autonomic Nervous System in Variant Angina

Vasospasm has been convincingly demonstrated in variant angina[4] and myocardial infarction,[6,7] although its underlying mechanism remains unknown. Early workers, such as Monakhov,[24] hypothesized autonomic dysfunction. In the 12 previously reported cases referred to by Prinzmetal et al.[2] when they delineated the syndrome in 1959, the angina was attributed to tobacco, hypoglycemia, nightmares and other causes. More recently, attention has returned to the autonomic nervous system, but the issue remains undecided, because attacks of angina have been said to be provoked by sympathomimetic (alpha) stimulation[12] and parasympathetic stimulation,[9,25] as well as parasympatholytic agents.[11] Therapeutic efficacy has been claimed for propranolol,[26] phenoxybenzanine,[12] atropine[25] and nylidrin.[2]

Lack of generalized increase in sympathetic outflow: The investigations of autonomic function in our three patients do not support the concept of a generalized increase in sympathetic outflow in variant angina. Urinary excretion of catecholamines and their metabolites was within the normal range. Baseline and stimulated plasma levels of norepinephrine, epinephrine and dopamine were normal. The results of physiologic maneuvers affecting cardiovascular function by way of the autonomic nervous system were normal. Finally, it was possible in two of our three patients to sample blood for catecholamines at the onset and termination of spontaneous S-T elevation. In both patients, catecholamines remained near baseline level. Because circulating norepinephrine was threefold greater with upright posture (in the absence of pain) and fivefold greater with treadmill exercise (again in the absence of pain), elevation of plasma norepinephrine cannot account for the phenomenon of variant angina observed in our patients.

Congruent with this is the observation that episodes of angina in our patients were not associated with changes in blood pressure or heart rate. Others[4,7,27–29] have observed this during extensive hemodynamic monitoring at cardiac catheterization or in the coronary care unit. The view is further strengthened by the observation in Patient 1 that venous tone was not altered at the onset of an episode of spontaneous S-T elevation. We interpret this to mean that there is no generalized increase in sympathetic outflow associated with the initiation of attacks of variant angina.

Vascular hyperreactivity with local vasoconstriction: Germane to this discussion is the effect of autotransplantation. This procedure has been investigated in the treatment of variant angina[30] with one subject experiencing relief of symptoms. Nevertheless, that patient had persistence of vasospasm in spite of the interruption of autonomic fibers to the coronary artery. While such a result could be interpreted to mean a regrowth of autonomic fibers, it may mean that the key to coronary vasoconstriction lies in local pathophysiology at the level of the vessel itself, independent of central sympathetic outflow. The fact that alpha adrenergic blockade reduces the attack rate in variant angina[25] does not prove that excess alpha activity is the cause of this disease, any more than modest blood pressure reduction with alpha blockade proves that excessive sympathetic activity causes hypertension. The association of Raynaud's phenomenon with variant angina, as seen in Patient 1, has been previously reported.[31,32] This association may mean that vascular hyperreactivity exists in other vessels in the same patient, but the true significance remains unknown.

Pharmacologic Therapy

Lack of propranolol effect: It has been suggested[33] that propranolol is contraindicated in variant angina because beta adrenergic blockade would counteract beta-mediated vasodilatation and leave alpha-mediated vasoconstriction unopposed, but some investigators[26] have found a beneficial effect in practice. In Patient 1, the administration of propranolol in a dosage of 160 mg every 6 hours seemed to lengthen the average duration of S-T segment elevation, although the total number of episodes remained approximately the same. In the other two patients, no such trend was evident. The lack of this effect in these patients and even in Patient 1 at a different time in his course suggests that etiologic mechanisms may vary from patient to patient or from time to time or that the same mechanism may vary in its susceptibility to modification. At the very least, these data suggest a need for caution in use of this agent.

Spontaneous fluctuations in severity—relation to nitrate and other drug trials: Perhaps the most important observation of this study, although not a new one, is that the syndrome of vasospastic angina has marked spontaneous fluctuation in severity. In Patient 1, there has been no recurrence of symptoms for 18 months. It has been suggested that relief of pain is usually seen after myocardial infarction, but there was no evidence for myocardial infarction in our patients. This important feature of variant angina was noted previously by MacAlpin et al.[34] in 1973. Recognition of this variability in course is obviously critical to the design and understanding of drug trials directed at variant angina, and should dictate controlled trials. Because short-acting nitrates are generally quite effective in aborting individual episodes of S-T elevation, they can be used intermittently, while longer-acting agents are

evaluated for their effect in decreasing the number of spontaneous episodes. Because many episodes are brief and asymptomatic, continuous monitoring may be important if valid conclusions are to be drawn. Without such monitoring and without blinded crossover protocols, we would clearly have been misled in the present study, because two patients were discharged free of episodes of S-T elevation and the third had significant improvement. Further carefully controlled and blinded drug trials will be necessary to determine optimal therapy for this disease.

Acknowledgment

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Hypertrophic Cardiomyopathy and Transmural Myocardial Infarction Without Significant Atherosclerosis of the Extramural Coronary Arteries

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Clinical and morphologic features of transmural myocardial infarction (associated with insignificant or absent atherosclerosis of the extramural coronary arteries) are described in seven patients with hypertrophic cardiomyopathy. Marked chronic congestive heart failure associated with supraventricular arrhythmias occurred in six of the seven patients, each of whom had no or mild left ventricular outflow tract obstruction under basal conditions. No patient had typical angina pectoris, and only one patient had clinically evident acute myocardial infarction. Infarction may have caused cardiac arrest in one other patient, but was "silent" in the remaining five patients.

At necropsy, six of the seven patients had extensive myocardial scarring involving the ventricular septum, left ventricular free wall and one or both left ventricular papillary muscles; in four patients portions of the right ventricular wall were also scarred. Six patients had dilated ventricular cavities, including two who were known to have nondilated ventricular cavities earlier in their clinical course.

It is concluded that transmural myocardial infarction in the absence of significant coronary atherosclerosis is a not uncommon finding (prevalence rate 15 percent) in a population of patients who had died from hypertrophic cardiomyopathy. Although transmural infarction is possibly a secondary event, it more likely contributes causally to the clinical deterioration of some patients with hypertrophic cardiomyopathy, leading to ventricular dilatation and progressive fatal cardiac failure.

Patients with hypertrophic cardiomyopathy often complain of chest pain (which may be typical or atypical of classic angina pectoris) and have electrocardiograms suggesting myocardial damage or ischemia.[1–7] Some of these patients have associated coronary arterial atherosclerosis[8–13] that may cause acute myocardial infarction.[14] In addition, previous necropsy studies[15–17] of hearts of adult patients with hypertrophic cardiomyopathy have shown that relatively small areas of interstitial or replacement fibrosis are commonly present in the left ventricular wall (particularly the subendocardial region and papillary muscles). However, it has not been appreciated that transmural myocardial infarction may occur in patients with hypertrophic cardiomyopathy who do *not* have significant coronary atherosclerosis or that it may play a role in the natural history of such patients with hypertrophic cardiomyopathy. This report describes the clinical and morphologic features of seven patients with hypertrophic cardiomyopathy and transmural myocardial infarction unassociated with significant atherosclerotic narrowing of the extramural coronary arteries.

Methods

Selection of patients: The necropsy records of the National Heart, Lung, and Blood Institute from 1958 to 1978 were reviewed. Eighty-two patients over the age of 10 years whose hemodynamic, angiographic, echocardiographic and ne-

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cropsy findings were consistent with the diagnosis of hypertrophic cardiomyopathy[3–5,18–21] were identified. Thirty-two patients who had undergone septal myotomy-myectomy, one patient who had cardiac transplantation and one patient who had mitral valve replacement were excluded from the analysis. Of the remaining 48 patients who had not undergone operation, 7 (15 percent) were judged by gross inspection of the heart to have *transmural* myocardial scarring (that is, a healed myocardial infarct) of the left ventricle, and they constitute the study group. None of these seven patients had significant atherosclerosis of any of the four major extramural coronary arteries. The patients ranged in age from 12 to 60 years (median 33).

Echocardiographic studies: Echocardiograms were performed with a 2.25 megahertz, 1.2 cm diameter Aerotech transducer connected to either a modified Ekoline-20A or a Hoffrel 201 ultrasonic unit employing methods previously described.[18] The thickness of the ventricular septum was measured below the tips of the mitral valve leaflets just before atrial systole; posterior left ventricular wall thickness was measured at the level of the tips of the mitral valve leaflets during the same phase of the cardiac cycle. End-diastolic and end-systolic left ventricular transverse dimensions were taken as the maximal and minimal dimensions, respectively, with the ultrasonic beam passing through the left ventricle slightly below the tips of the mitral valve leaflets.

Necropsy studies: *The location of myocardial scars* was assessed by gross inspection of the heart. The location of the left ventricular free wall scars was designated as either anterior or posterior, either apical or basal and either transmural or nontransmural[22] (Fig. 1).

Measurements were made of the maximal thickness of the ventricular septum, left and right ventricular free walls and the posterior left ventricular free wall at a level corresponding with the distal margin of the posterior mitral leaflet.[23] These measurements were obtained, when possible, in areas of the ventricular walls relatively free of scarring. The size of the ventricular and atrial cavities was judged by visual inspection to be either normal or dilated.

The coronary arteries were excised *intact* in four patients, and sectioned by a method described elsewhere.[24] Briefly, the excised arteries were cut at 5 mm intervals at right angles to the longitudinal axes of the vessels, and each 5 mm long segment was processed, embedded in paraffin and cut. A single Movat-stained histologic section was examined from each 5 mm segment. In the other three patients, the extramural coronary arteries were studied in the intact specimen by making multiple cross sections of the vessels (about 5 mm apart) and viewing the lumens grossly.

Results

Clinical findings and course (Table I): None of the seven patients had typical angina pectoris. Two patients (Cases 3 and 4) experienced occasional chest discomfort that was probably of cardiac origin but was not typical of angina pectoris; Patient 3 had a 5 year history of retrosternal pain precipitated by palpitations, and Patient 4 had a 7 year history of periodic, prolonged retrosternal discomfort. Only Patient 3 had a clinical episode consistent with acute myocardial infarction; 3 months before death this patient experienced severe substernal chest pain that lasted for 1 hour, radiated to both arms and was associated with diaphoresis, nausea, vomiting and fine rales in the left lung and marked elevations in serum myocardial enzyme levels (glutamic oxaloacetic transaminase 630, lactic dehydrogenase 3,580 and creatine kinase 2,475 units; a pericardial friction rub and paroxysmal atrial tachycardia were present on the following day.

DEFINITION OF MYOCARDIAL INFARCTS

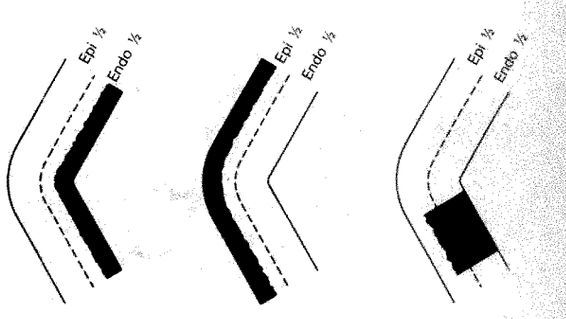


FIGURE 1. Definition of myocardial infarcts. *Subendocardial* infarcts involve no more than the inner one-half of the ventricular wall. *Subepicardial* infarcts involve no more than the outer one-half of the ventricular wall. *Transmural* infarcts involve more than the inner one-half of the ventricular wall. Endo ½ and Epi ½ = endocardial and epicardial one-half of the ventricular wall thickness, respectively.

In six of the seven patients the clinical course was characterized by profound chronic congestive heart failure with cardiac enlargement (Fig. 2a, 2b, 3b and 4a) and supraventricular arrhythmias. Two of these patients (Cases 5 and 6) experienced progressive and steady clinical deterioration over a period of several years. Two patients (Cases 3 and 4) manifested rapid symptomatic deterioration 1 week before death; two other patients (Cases 2 and 7) had marked changes in their clinical condition 3 months before death. The remaining patient (Case 1) was asymptomatic before experiencing a cardiac arrest at age 12 years; he subsequently survived for 6 weeks with evidence of severe cerebral anoxia. The transmural myocardial scarring was significantly more common in our patients who died of congestive heart failure (6 of 14 [43 percent]) than in those who died suddenly (1 of 22 [4 percent]; $P < 0.025$) (Fig. 5).

Two patients (Cases 2 and 6) (Table II) had marked congestive heart failure and ventricular dilatation in the latter stages of their illness (as assessed with echocardiography or at necropsy) but had a nondilated heart by angiography 8 and 9 years earlier, respectively (Fig. 4, b and c). This evolution from a nondilated hyperdynamic left ventricle to a dilated poorly contractile ventricle was associated with symptomatic deterioration.

Physical findings: One patient (Case 1) had not had an adequate cardiac physical examination before death. Systolic ejection murmurs were present under basal conditions in each of the other six patients; these murmurs were heard loudest at the lower left sternal border and apex. In two patients (Cases 3 and 5) the murmur was grade 3/6, suggesting the presence of marked left

TABLE I

Hypertrophic Cardiomyopathy and Transmural Myocardial Infarction: Clinical Findings

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (yr) & sex	12M	19F	20F	33M	41F	50F	60M
NYHA class*	I	IV‖	II	III	IV	III	IV‖
Chest pain	0	0	+	+	0	0[c]	0[e]
Duration of illness (yr)†	0	7 mo	10	7	3	25[d]	11
AMI	0	0	+	0	0	0	0
Pressures (mm Hg)							
LVOT (PSG)							
Basal	—	0	40	0	0	0	—[f]
Provoked	—	60	55	0	—	7	—
LV S/D	—	130/-	160/10	100/16	85/26	110/23	—
SA S/D	—	130/90	120/60	120/80	90/55	115/65	—
PA S/D	—	—	40/-	28/10	50/25	27/11	—
Other cardiac findings	None	A Fl	SVT; sev MR	SVT (occ); CVA age 28	AF; sev MR	AF	AF
Treatment with propranolol (no. of yr. before death)	0	8	3	6	0	0	0
Mode of death							
CHF		+¶	+[a]	+[a]	+[b]	+	+[g]
Sudden	+‡						
Family history of premature cardiac death	+§	+	0	0	0	+§	+

* Assessment made arbitrarily 1 month before death.
† From the time symptoms were first noted consistently.
‡ Collapsed while jogging; ventricular fibrillation documented; patient survived 6 weeks with anoxic brain damage.
§ "Malignant" hypertrophic cardiomyopathy.[26]
‖ Rapid clinical deterioration occurred 3 months or less before death (from functional class II to class IV).
¶ Patient's terminal illness was characterized by left ventricular failure, fever, nausea, diarrhea, abdominal pain, weakness, dyspnea, atrial flutter and hyponatremia.
[a] Acute deterioration due to congestive heart failure 3 days before death.
[b] History of marked congestive heart failure thought to be due to severe rheumatic mitral regurgitation; however, at operation the mitral valve was noted to be normal; the patient died 1 day after operation because of pulmonary embolus with infarction.
[c] Brief stabbing left precordial pain not thought to be cardiac in origin.
[d] Including a 10 year period (between age 30 and 40 years) during which there was a spontaneous loss of symptoms.
[e] Chest pain occurred before but not after age 43.
[f] However, absence of systolic anterior motion of the anterior mitral leaflet on echocardiography (under basal conditions) and absence of a cardiac murmur (under basal conditions or with provocative maneuvers) indicated that obstruction to left ventricular outflow was not present in this patient.
[g] Patient's terminal illness (during last 10 weeks of life) was characterized by left ventricular failure with pulmonary edema, paroxysmal atrial fibrillation, hypotension, periods of bradycardia and renal failure; pulmonary arterial wedge pressure was 28 mm Hg; pressor agents were required to maintain systolic blood pressure at 90–110/60–75 mm Hg.
+ = present; 0 = absent; — = data not available.
AF = atrial fibrillation; A Fl = atrial flutter; AMI = acute myocardial infarct; CHF = congestive heart failure; CVA = cerebrovascular accident; 1° AVB = first degree atrioventricular block; LV = left ventricle; LVOT = left ventricular outflow tract; MR = mitral regurgitation; NYHA class = New York Heart Association functional class; occ = occasional; PA = pulmonary artery; PSG = peak systolic gradient; RVH = right ventricular hypertrophy; SA = systemic artery; S/D = systolic/diastolic; sev = severe; SVT = supraventricular tachycardia.

TABLE II

Serial Clinical Data in Two Patients With Hypertrophic Cardiomyopathy and Transmural Myocardial Infarction: Progression From Nondilated to Dilated Left Ventricle

	Patient 2		Patient 6	
	I	II	I	II
Age (yr)	11	19	41	50
NYHA class	II	IV	II	III
Systolic ejection murmur (grade)	2/6	2/6*	2/6	None*
Cardiothoracic ratio (X-ray)	0.53	0.63	0.50	0.62
LVOT gradient (mm Hg) (basal/provoked)	0/60	0*	0/7	0*
$LVID_S/LVID_D$ (mm)	—	50/57†	—	61/67†
Ejection fraction (%)	90 (angio)	30 (echo)	65 (angio)	25 (echo)

* Absence of systolic anterior motion of the anterior mitral leaflet on echocardiography (under basal conditions) and absence of a loud cardiac murmur (grade 3/6 or higher) under basal conditions or with provocative maneuvers indicated that obstruction to left ventricular outflow was not present.
† This patient died within 1 year of the most recent cardiac evaluation and showed ventricular dilatation at necropsy.
— = data not available.
Angio = angiography; I = initial cardiac evaluation; II = most recent cardiac evaluation; echo = echocardiography; $LVID_D$ and $LVID_S$ = left ventricular internal dimension in diastole and systole, respectively (as assessed with echocardiography); LVOT = left ventricular outflow tract; NYHA class = New York Heart Association functional class.

ventricular outflow obstruction. In four patients the murmur was grade 1-2/6, suggesting minimal obstruction to outflow. The second heart sound was single in two patients and was physiologically split in four patients. A third heart sound was heard in two patients, a fourth heart sound in two patients and both third and fourth heart sounds in two patients.

Echocardiographic findings: The echocardiographic data obtained in four of the seven patients are summarized in Table III. In each patient both the diastolic and systolic left ventricular internal dimensions were increased over normal. Hence, left ventricular ejection fraction (as well as percent fractional shortening) was abnormally decreased in each patient (Fig. 6).

Electrocardiographic findings: The electrocardiograms were abnormal in each of the six patients whose tracings were obtained (Table IV) (Fig. 3c, 4d, 7, 8a and 9c). Analysis of the electrocardiograms obtained in the latter stages of each patient's illness (within 1 year of death) disclosed that the most consistent abnormality was diffuse T wave alterations (usually symmetric T wave inversion). Deep (more than 4 mm) or wide (more than 0.04 second) Q waves were present in each of the six patients, primarily in "lateral" electrocardiographic leads (that is, leads I, aVL, V_5 and V_6) and were usually associated with abnormally small R waves in the left precordial leads. Conduction abnormalities (intraventricular conduction defect, left anterior hemiblock or first degree atrioventricular block) were also present in five patients. Of 25 patients in the original study group *without* transmural myocardial scars or significant coronary arterial narrowing (and whose electrocardiograms were available for analysis), 10 also showed deep wide Q waves in one or more leads. However, the prevalence of Q waves in these patients was significantly less than that in patients with transmural scarring ($P < 0.05$).

Electrocardiographic evidence of left ventricular hypertrophy was present in only one patient (Case 6),

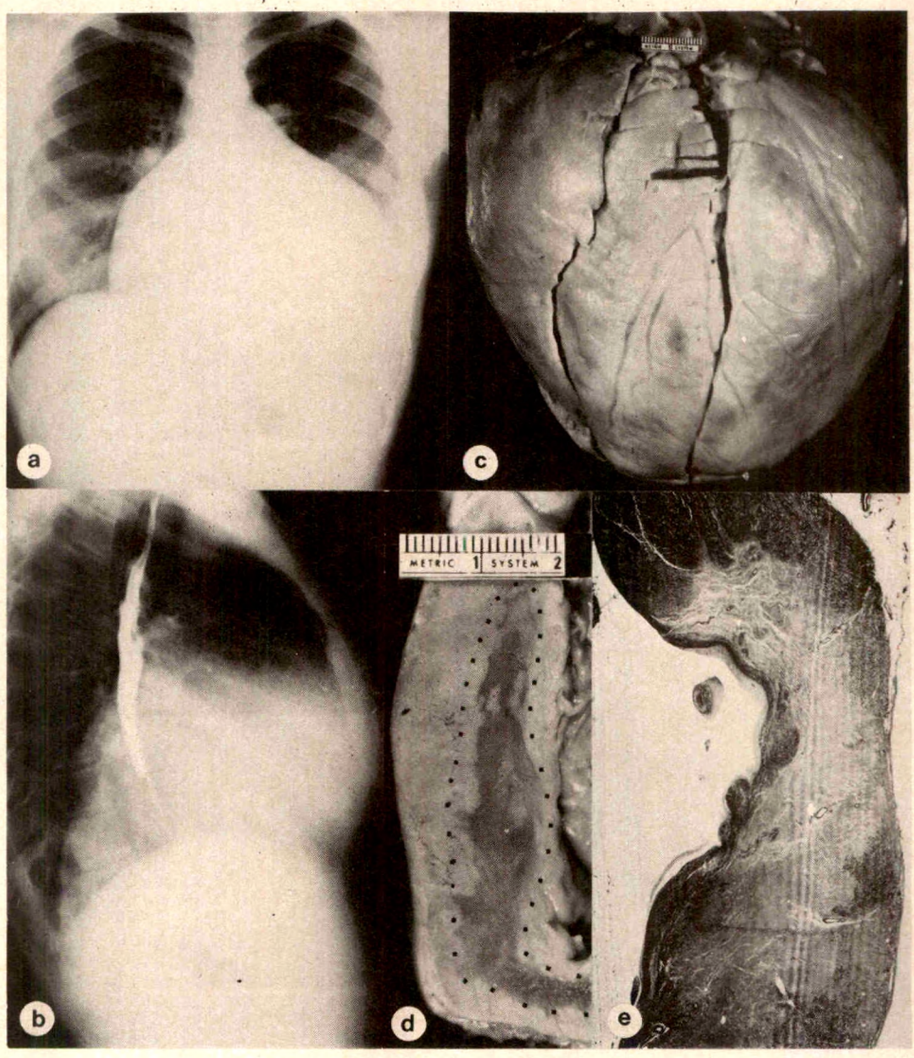


FIGURE 2. Case 3. Radiographic and necropsy findings. **a** and **b**, posteroanterior and lateral chest radiographs, respectively, taken 5 years before death and showing marked cardiac enlargement (cardiothoracic ratio = 0.73). **c**, exterior view of heart showing massive cardiomegaly (heart weight = 1,250 g). **d**, longitudinal cut of ventricular septum showing extensive scarring (**outlined by dots**); **e**, longitudinal section of basal left ventricular free wall showing an extensive scar that involves the entire thickness of the wall.

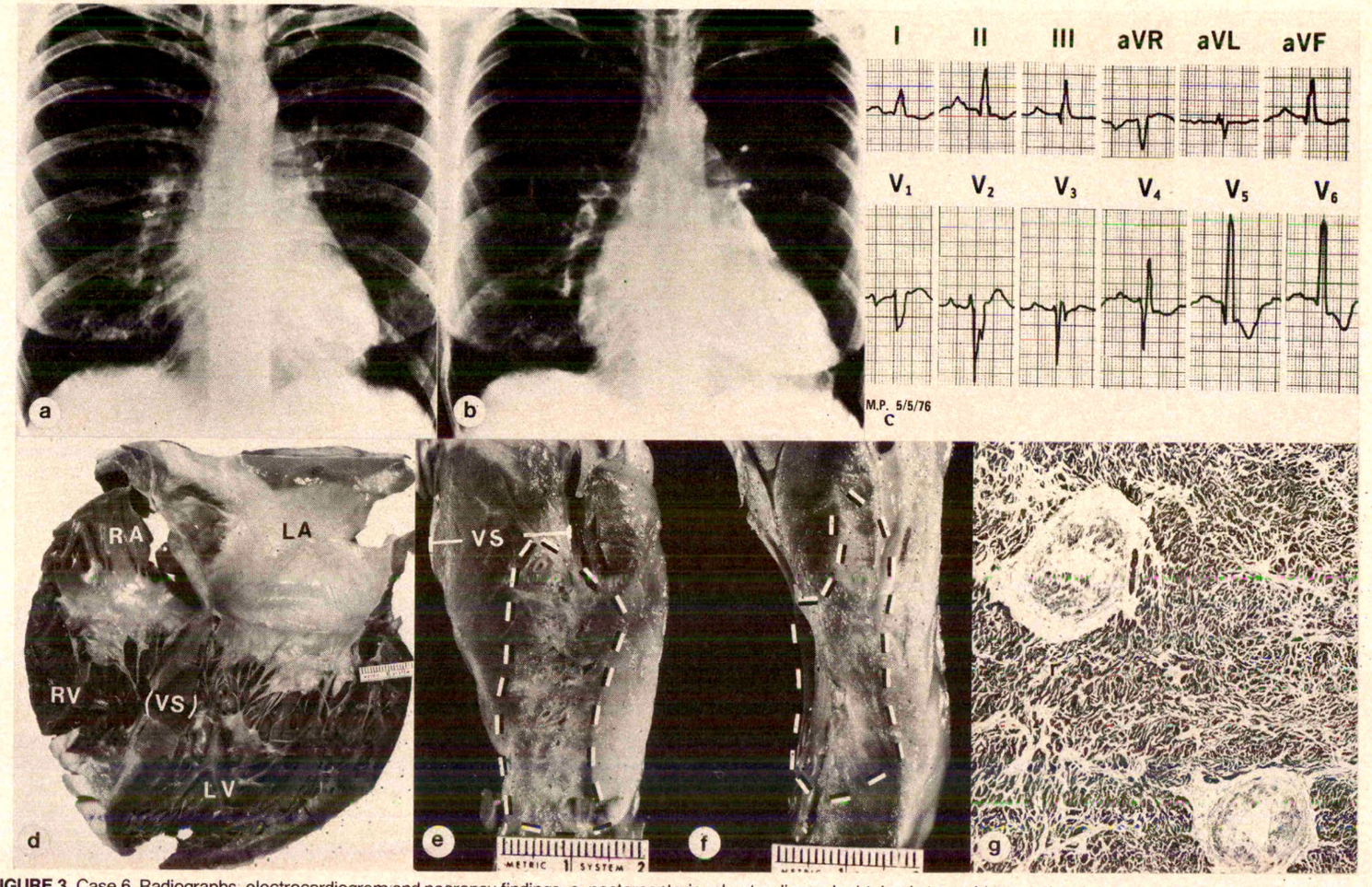


FIGURE 3. Case 6. Radiographs, electrocardiogram and necropsy findings. **a,** posteroanterior chest radiograph obtained at age 41 years showing a normal-sized heart (cardiothoracic ratio = 0.50). **b,** posteroanterior chest radiograph obtained 9 years later showing a marked increase in heart size (cardiothoracic ratio = 0.62). **c,** electrocardiogram showing left ventricular hypertrophy with "strain," left atrial abnormality, intraventricular conduction defect, first degree atrioventricular block, Q wave in lead V_5, "poor R wave progression" across the anterior precordium and diffuse S-T segment and T wave abnormalities. **d,** longitudinal section of the heart showing dilatation of left ventricle (LV), right ventricle (RV), left atrium (LA) and right atrium (RA); the ventricular septum (VS) is disproportionately thickened with respect to the left ventricular free wall. **e,** longitudinal cut of ventricular septum (VS) showing extensive transmural scarring (**outlined by broken line**). **f,** longitudinal cut of left ventricular free wall showing a transmural scar (**outlined by broken line**). **g,** section of a portion of ventricular septum showing abnormal intramural coronary arteries with thickened walls and narrowed lumens (hematoxylin-eosin ×35, reduced by 25 percent).

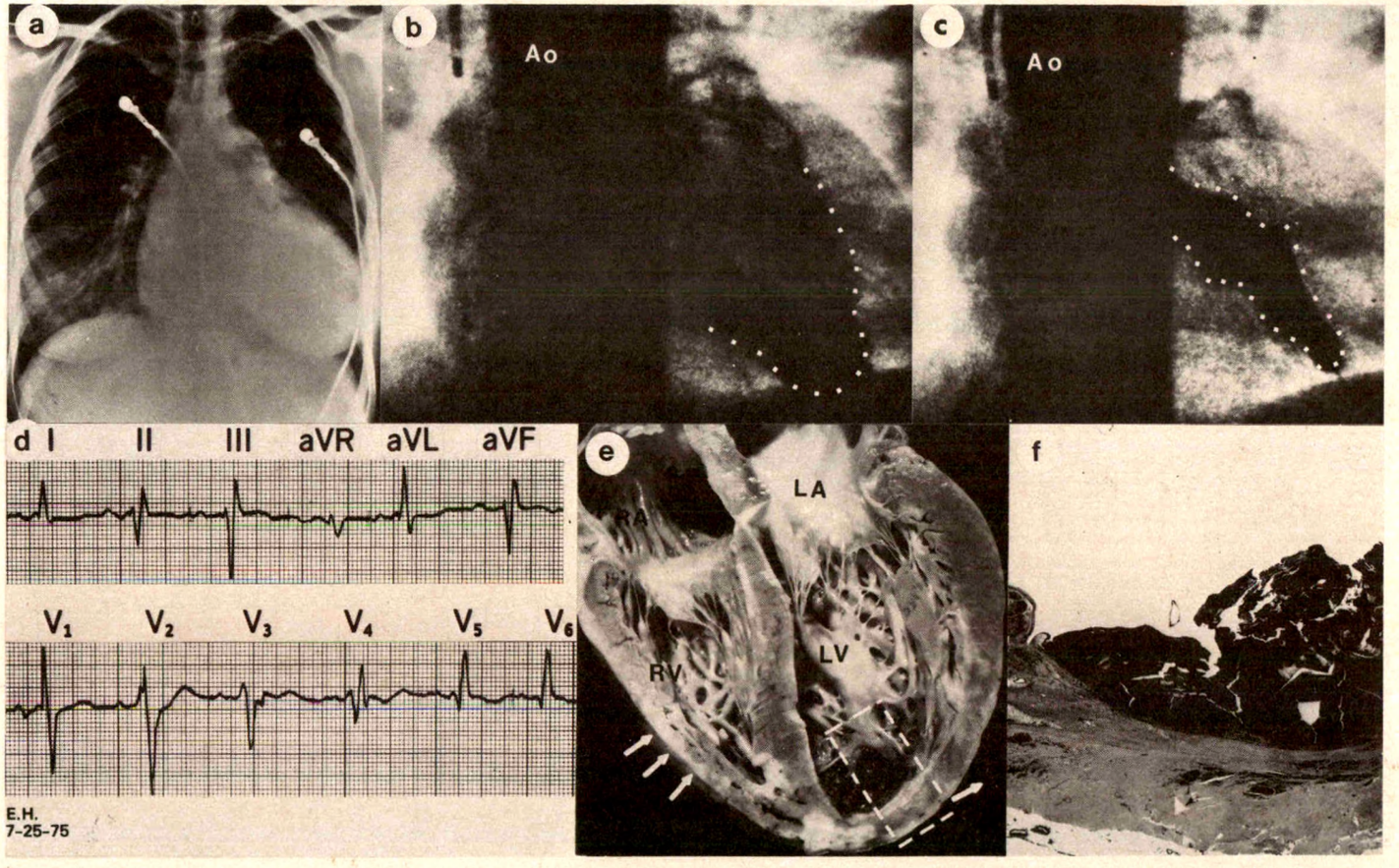


FIGURE 4. Case 2. Chest radiograph, angiocardiograms, electrocardiogram and necropsy findings. **a,** posteroanterior chest radiograph obtained 1 month before death shows marked cardiac enlargement (cardiothoracic ratio = 0.64). **b,** left ventricular angiocardiogram in end-diastole (obtained 8 years before death) showing normal ventricular volume and marked thickening of the ventricular wall; the **dotted line** outlines left ventricular cavity; Ao = aorta. **c,** left ventricular angiocardiogram in end-systole showing small ventricular volume; the **dotted line** outlines the left ventricular cavity. **d,** electrocardiogram shows the left atrial abnormality and T wave abnormalities; the tall R wave in lead V_1 reflects hypertrophy of either the ventricular septum or the right ventricular wall. **e,** longitudinal section of the heart with the anterior half removed showing considerable dilatation of both the right (RV) and the left ventricular (LV) cavities and concentric (symmetric) ventricular hypertrophy; transmural scarring of the left ventricular apex and right ventricular wall (**arrows**) is evident; LA = left atrium; RA = right atrium. **f,** extensive transmural scarring of left ventricular apex with superimposed thrombus; from the portion of apical scarring outlined by broken line in **e,** but shown at higher magnification (hematoxylin-eosin ×3, reduced by 25 percent).

although Patients 2 and 3 had shown this abnormality earlier in their clinical course. In particular, the changes in electrocardiographic pattern demonstrated by Patient 3 suggested progressive ventricular scarring over a 5 year period (Fig. 7); however, the possibility also exists that these abnormalities (deep Q waves in the lateral precordial leads and tall R waves in the right precordial leads) were due to increased forces of depolarization in the greatly thickened ventricular septum.[1]

Hemodynamic findings: Five patients underwent cardiac catheterization, 6 months to 10 years before death (Table I). A left ventricular outflow gradient of 40 mm Hg was present under basal conditions in one patient (Case 3); gradients were absent under basal conditions in the other four patients (although one of these had a 60 mm Hg gradient with isoproterenol infusion). One additional patient (Case 7), who had not undergone hemodynamic study, had an echocardiogram recorded 3 months before death that showed no systolic anterior motion of the anterior mitral leaflet under basal conditions, a finding consistent with the absence of outflow obstruction.[21] In two patients without outflow obstruction who had undergone hemodynamic study more than 5 years before death an echocardiogram recorded within 18 months of death showed no evidence of systolic anterior motion of the anterior mitral leaflet. This finding suggested the continued absence of outflow obstruction in these patients.

Genetic transmission: Genetic transmission of hypertrophic cardiomyopathy was demonstrated in first degree relatives of each of the seven patients. In four of these patients at least one first degree relative died prematurely of hypertrophic cardiomyopathy; in two of these families premature death occurred unusually frequently (that is, "malignant" hypertrophic cardiomyopathy[26] appeared to be present). In the families of the other three patients, at least one surviving relative had clinically evident hypertrophic cardiomyopathy. The only patient (Case 2) with concentric ventricular hypertrophy (demonstrated both with echocardiography and at necropsy) had a brother with hypertrophic cardiomyopathy whose sudden death at age 13 years was the first definitive manifestation of cardiac disease[27]; also, the patient's mother manifested asymmetric septal hypertrophy (septal-free wall thickness ratio of 1.7) on echocardiography. In addition, two patients (Cases 1 and 5) had the marked disorganization of cardiac muscle cells in the ventricular septum (involving 5 percent or more of the tissue section) that is characteristic of patients with hypertrophic cardiomyopathy[28]; in the other five patients a reliable assessment of the extent of septal disorganization could not be made because of widespread replacement fibrosis.

Necropsy Findings (Table V)

Gross pathology: Heart weights were increased compared with normal values[31] in each patient. In five of the seven hearts the ventricular septum was asymmetrically thickened with respect to the left ventricular

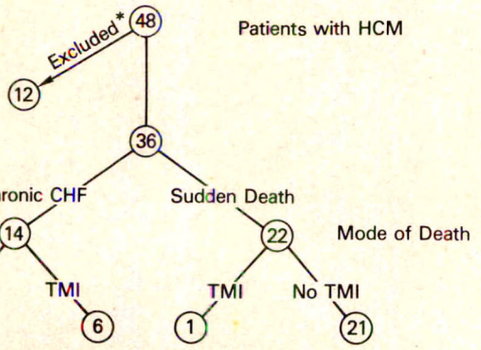


FIGURE 5. Diagram showing prevalence of transmural myocardial infarction (TMI) among patients with hypertrophic cardiomyopathy (HCM) who died suddenly and those who experienced chronic congestive heart failure (CHF). * = patients with hemodynamically significant narrowing of at least one major coronary artery and patients who died of noncardiac causes.

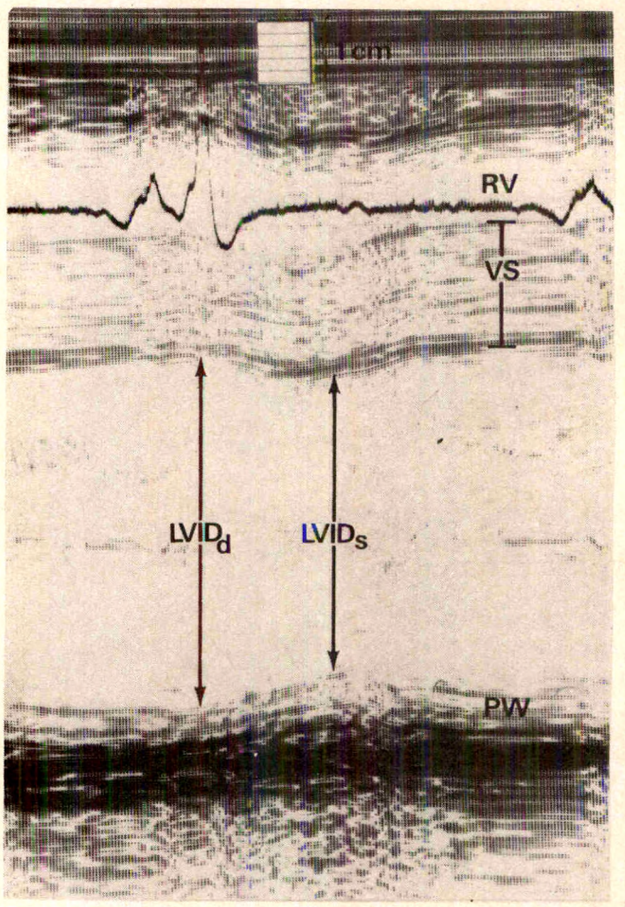


FIGURE 6. Case 7. Echocardiogram recorded inferior to the level of the mitral leaflets. The left ventricular internal dimensions in both diastole ($LVID_d$) and systole ($LVID_s$) are increased. Other portions of the tracing showed somewhat greater internal dimensions. The ventricular septum (VS) is disproportionately thickened with respect to the posterior left ventricular free wall (PW). RV = right ventricle.

free wall (septal-free wall thickness ratio greater than or equal to 1.3) (Fig. 3d and 9b).[18,21] In the remaining two patients (Cases 2 and 4) the ventricular septum and left ventricular free wall were of equal thickness at necropsy (Fig. 4f). However, in Patient 4 the septal-free wall thickness ratio calculated during life with echocardiography was abnormal (1.4), thus confirming the diagnosis of hypertrophic cardiomyopathy (with asymmetric septal hypertrophy). Such discrepancies between septal-free wall thickness ratios obtained during life and at necropsy have been explained previously.[32] In Patient 2 (whose mother had a septal-free wall thickness ratio of 1.7 on echocardiography) the echocardiographic septal-free wall thickness ratio was 1.0; this patient therefore had genetically transmitted hypertrophic cardiomyopathy with concentric (symmetric) ventricular hypertrophy.[33]

The left and right ventricular cavities were dilated in six of the seven patients (Fig. 3d and 4f) and very extensively in two of these patients. Only Patient 5, who had a relatively discrete myocardial scar, had ventricular cavities of normal size. Thrombi were present in the

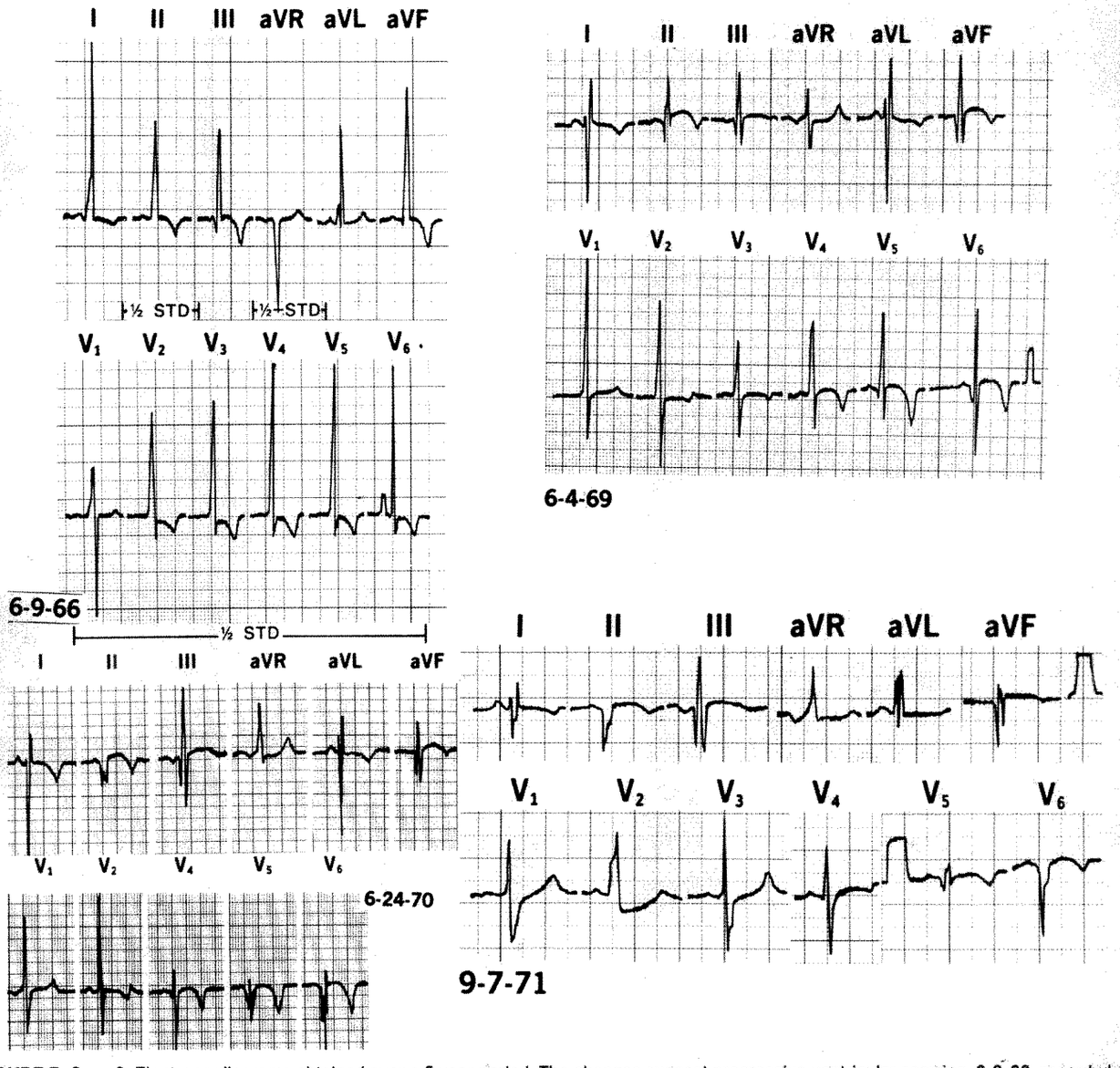


FIGURE 7. Case 3. Electrocardiograms obtained over a 5 year period. The changes suggest progressive ventricular scarring. **6-9-66,** recorded at age 16 years, showing strikingly increased precordial voltages (up to 82 mm), left ventricular "strain" pattern and diffuse T wave inversion. **6-4-69,** the tracing recorded at age 19 has changed substantially and now shows right axis deviation, a tall R wave in right precordial leads (suggestive of right ventricular or ventricular septal hypertrophy), greatly diminished left precordial R wave voltages, Q waves in leads II, III, aVF and V_6 and more marked T wave inversion in leads V_5 and V_6. **6-24-70,** in the tracing recorded at age 20, the left precordial R wave voltages are virtually absent and Q waves are more prominent in leads II, III, aVF, V_5 and V_6. **9-7-71,** the tracing recorded at age 21 (1 month after an acute myocardial infarction), the R wave in lead V_1 is diminished and left or "unusual" axis deviation is present. STD = standardization.

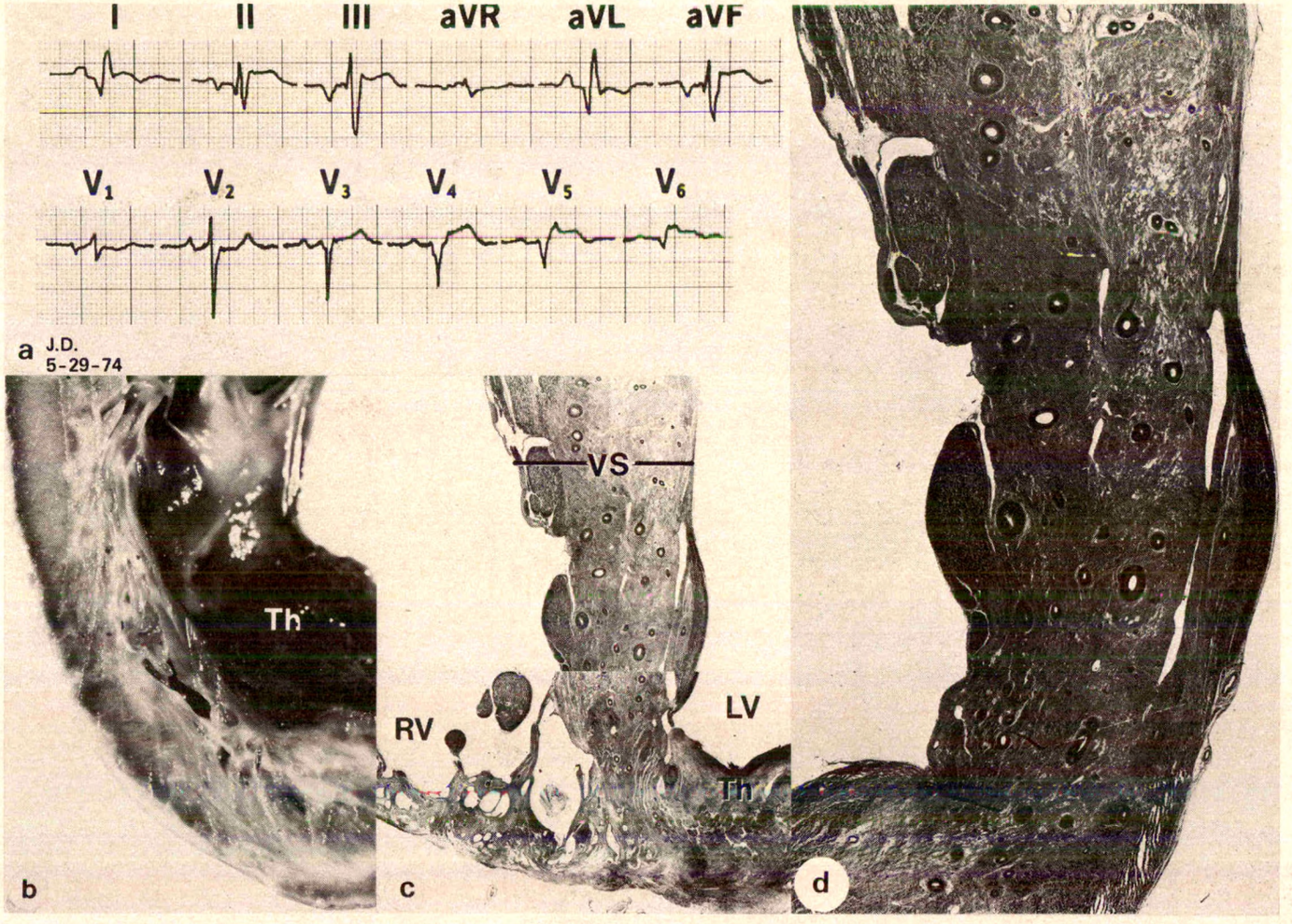


FIGURE 8. Case 4. Extensive transmural myocardial scarring. **a,** the electrocardiogram shows Q waves in leads I and aVL, diminished R wave voltage in the left precordial leads, an intraventricular conduction defect and diffuse T wave abnormalities. **b,** extensive scarring of the full thickness of the left ventricular free wall with superimposed mural thrombus (Th). **c,** composite microphotograph of a longitudinal section near the apex of the ventricular septum (VS) and contiguous areas of the right (RV) and left (LV) ventricular walls showing marked transmural scarring of both free walls and the septum; numerous abnormal intramural coronary arteries are present in the ventricular septum (elastic van Gieson stain X3, reduced by 25 percent). **d,** the area of ventricular septum shown in **c,** but at higher magnification; extensive scarring even involves areas adjacent to prominent abnormal intramural coronary arteries (elastic van Gieson stain X3, reduced by 25 percent).

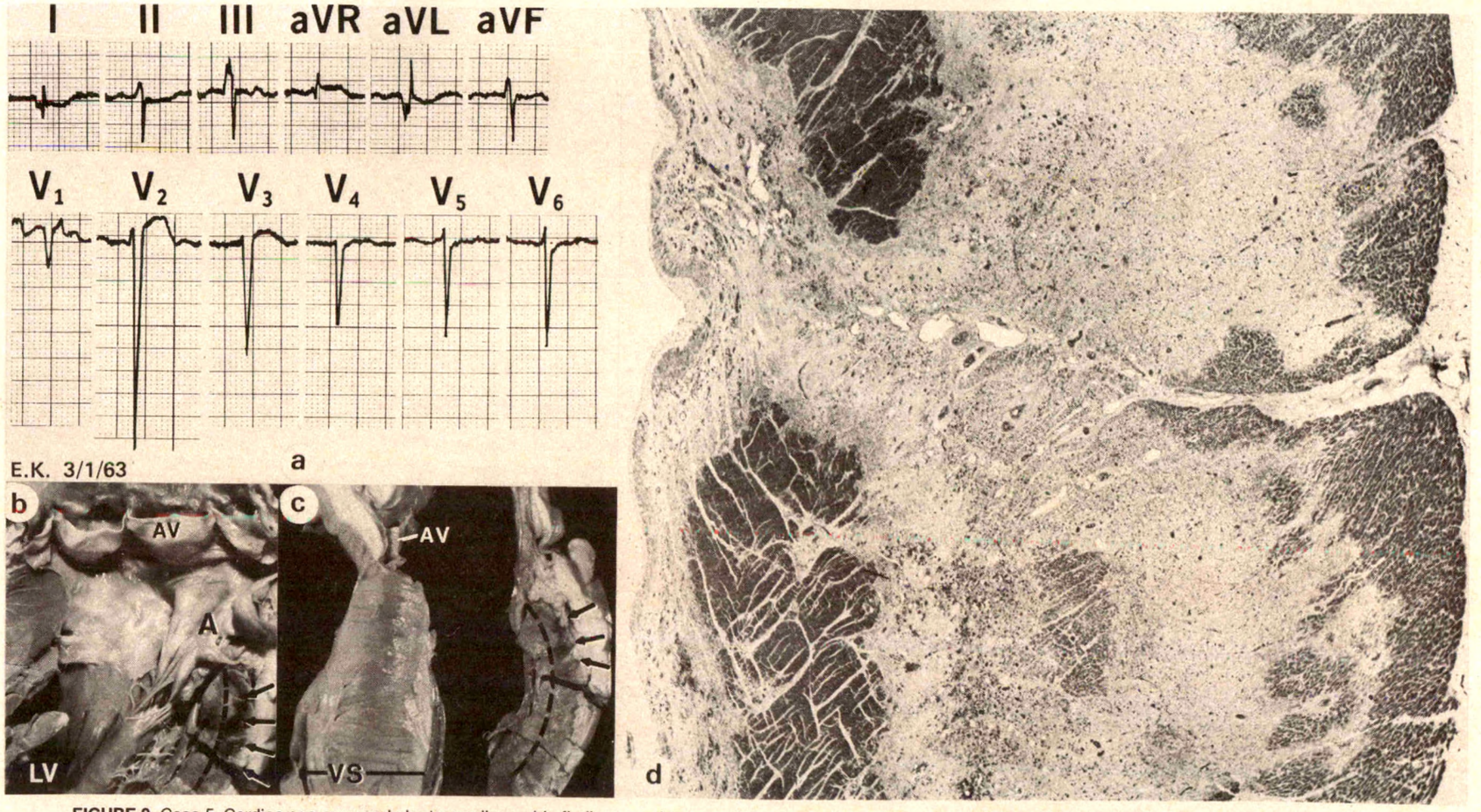


FIGURE 9. Case 5. Cardiac necropsy and electrocardiographic findings. **a,** electrocardiogram shows a left anterior hemiblock pattern, Q waves in leads I and aVL, diminished R wave voltage in the left precordial leads and diffuse S-T segment and T wave abnormalities. **b,** close-up view of left ventricular (LV) outflow tract showing endocardial mural plaque beneath the aortic valve (AV) and in direct apposition to the thickened anterior mitral leaflet (A), findings typical of hypertrophic cardiomyopathy; a subepicardial infarct is evident in the basal left ventricular free wall (**arrows**); the **broken line** serves to divide the inner from the outer halves of the ventricular wall. **c,** longitudinal cuts of ventricular septum (VS) and left ventricular free wall showing disproportionate thickening of the septum relative to the left ventricular free wall; an infarct in the basal subepicardial region of the left ventricular free wall (**arrows**) also is evident; the **broken line** serves to divide the inner from the outer halves of the ventricular wall; AV = aortic valve. **d,** histologic section of a portion of left ventricular free wall showing transmural replacement fibrosis (from an area of left ventricular free wall not shown in **b** or **c**) (hematoxylin-eosin ×21, reduced by 34 percent).

TABLE III

Hypertrophic Cardiomyopathy and Transmural Myocardial Infarction: Echocardiographic Findings*

Case no.	Age (yr) & sex	VS (mm)	PW (mm)	VS/PW	$LVID_d$ (mm)	97.5% Prediction Limit† $LVID_D$ (mm)	$LVID_s$ (mm)	97.5% Prediction Limit† $LVID_s$ (mm)	EF‡ (%)	FS§ (%)
2	19F	14	14	1.0	57	52	50	35	32	12
4	33M	16	13	1.2‖	55	54	42	36	55	24
6	50F	15	10	1.5	67	53	61	35	25	9
7	60M	19	9	2.1	58	52	50	34	36	14

* Includes data from only the echocardiogram obtained closest to the time of death.
† That value below which about 97.5 percent of the normal population lies; both $LVID_D$ and $LVID_s$ are a linear function of age and body surface area.[25]
‡ The 2.5 percent prediction limit (that value above which about 97.5 percent of the normal population lies) was 67 percent for each patient because ejection fraction is not a function of age or body surface area.[25]
§ The 2.5 percent prediction limit was 30 percent for each patient because percent fractional shortening is not a function of age or body surface area.[25]
‖ Another echocardiogram recorded 9 months earlier showed asymmetric septal hypertrophy (ventricular septal thickness 18 mm, posterior left ventricular free wall thickness 13 mm and septal-free wall thickness ratio 1.4).
EF = left ventricular ejection fraction; FS = percent fractional shortening; $LVID_D$ and $LVID_s$ = left ventricular internal dimension in diastole and systole, respectively; PW = posterior left ventricular free wall thickness; VS = ventricular septal thickness; VS/PW = ventricular septal to posterior left ventricular free wall thickness ratio.

ventricular cavities of four patients (left ventricle in one, right ventricle in one and both ventricles in two) (Fig. 4f and 8b); there was no evidence of ventricular thrombi in the three other patients with transmural scarring or in the 41 nonsurgically treated patients without transmural scarring.

Coronary arterial anatomy: At necropsy, none of the seven patients had atherosclerotic luminal narrowing greater than 75 percent of cross-sectional area[24] of any of the four major *extramural* coronary arteries. Most arteries were either free of atherosclerotic plaques or were narrowed less than 25 percent by plaques (Fig. 10 and 11). Patient 5 had an organizing clot (most likely an embolus) completely occluding the right coronary artery for a length of 3.5 cm; minimal atherosclerosis was present in the artery (Fig. 12, a to c).

In contrast, marked abnormalities of the *intramural* coronary arteries[34] were present in six of the seven patients (Fig. 3g and 8, c and d). These abnormal vessels had thickened walls (due to intimal proliferation or

TABLE IV

Hypertrophic Cardiomyopathy and Transmural Myocardial Infarction: Electrocardiographic Findings*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (yr) & sex	12M	19F	20F	33M	41F	50F	60M
Ventricular hypertrophy	–	R†	0‡	0	0	L	0
Diffuse T wave abnormalities	–	+	+	+	+	+	+
Q waves in leads							
I, aVL	–	0	0	+	+	0	+
V_5,V_6	–	+	+	+	0	+¶	+
II, III, aVF	–	0	+	0	0	0‖	0
IVCD	–	0†	0	+	0	+	0
LAH	–	0	+§	0	+	0	+
1°AVB	–	0	0	0	0	+	0
↓ R wave in left precordium	–	0	+	+	+	0	0
LAE	–	+	0	0	0	+	+

* The electrocardiogram recorded closest to the time of death (with the patient in a relatively stable clinical state) was used.
† The electrocardiographic pattern was also consistent with ventricular septal hypertrophy; left ventricular hypertrophy with "strain" and Wolff-Parkinson-White pattern were present 5 years previously.
‡ The patient showed substantial changes in the electrocardiographic pattern over an 11 year period (see Fig. 7); initially the electrocardiogram showed marked left ventricular hypertrophy with "strain" and subsequently a pattern consistent with either right ventricular or ventricular septal hypertrophy.
§ Left axis deviation only.
‖ Lead V_5 only.
¶ Marked decrease in prominence of Q waves in leads II, III and aVF was noted 4 years before death.
+ = present; 0 = absent; – = data not available; ↓ = decreased.
1°AVB = first degree atrioventricular block; IVCD = intraventricular conduction defect; L = left; LAH = left anterior hemiblock; LAE = left atrial enlargement; R = right.

TABLE V

Hypertrophic Cardiomyopathy and Transmural Myocardial Infarction: Necropsy Findings

	Case 1 (A105-75)	Case 2 (A75-209)	Case 3 (A72-197)	Case 4 (A74-216)	Case 5 (A63-77)	Case 6 (A77-32)	Case 7 (A76-108)
Age (yr) & sex	12M	19F	20F	33M	41F	50F	60M
Heart weight (g)	270	530	1250[b]	580	530	550	530
Location of transmural infarcts							
VS	+	+	+	+	+	+[f]	+
LV free wall							
Anterior	0	+	+	+	0	+	+
Posterior	+	+	+	+	+	0	+
Basal	+	+	+	0	+	+	+
Apical	+	+	+	+	0	+	+
RV							
Anterior	+	+	+	+	0	0	0
Posterior	0	+	+	+	0	0	0
Basal	0	+	+	0	0	0	0
Apical	+	+	+	+	0	0	0
LV pap infarct							
AL	0	+	+	+	0	+	+
PM	+	+	+	+	+	+	0
Subepicardial infarct	0	0	+	0	+	0	+
Histologic age of infarcts[29,30]							
<1 mo	0	0	0	0	+	0	0
1–2 mo	0	0	+[c]	0	+	0	0
>2 mo	+	+	+	+	+	+	+
Coronary arteries							
Extramural*							
LAD	0–25%	26–50%	0–25%[d]	51–75%	0–25%	0–25%[d]	0–25%[d]
LCx	0–25%	0–25%	0–25%	0–25%	0–25%	0–25%	0–25%
LMCA	0–25%	0–25%	0–25%	0–25%	0–25%	0–25%	0–25%
RCA	0–25%	0–25%	0–25%	26–50%	0–25%	0–25%	0–25%
Intramural†							
VS	+	0	+	+	+	+	+
LV	0	0	+	0	+	+	+
RV	0	0	0	+	0	0	0
Ventricular wall thickness							
VS	18	13	42	15	25	15	14
Post LVFW‡	10	13	10	15	9	10	10
Max LFVW	13	14	19	15	13	10	12
RV	5	6	11	5	6	3	6
VS/Post LVFW	1.8	1.0§	4.2	1.0[e]	2.8	1.5	1.4
Cavity size							
LV	↑	↑‖	↑	↑	0	↑‖	↑
RV	↑	↑‖	↑	↑	0	↑‖	↑
LA	0	↑	↑	↑	↑	↑	↑
RA	0	↑	↑	↑	↑	↑	↑
VS plaque	0	+[a]	0	0	+	+[g]	0
Thickened AML	0	0	0	0	+	+	0
Thrombus							
LV	0	+	+	+	0	0	0
RV	0	+	+	0	0	+	0

* Percent cross-sectional area narrowing by atherosclerosis; narrowing of any extramural coronary artery that was greater than 75 percent of the vessel lumen was considered abnormal.[24]

† Intramural coronary arteries with thickened walls (evidenced by intimal proliferation, medial hypertrophy or both) and luminal narrowing.

‡ Measured behind the mid point of the posterior mitral leaflet at the level of the inferior margins of the mitral leaflets.

§ Echocardiogram recorded 1 month before death showed concentric ventricular wall thickening (ventricular septal and posterior left ventricular free wall thicknesses were each 14 mm); no earlier echocardiograms were available for analysis.

‖ Marked dilatation similar in magnitude to that present in dilated cardiomyopathy.

[a] In the form of a discrete linear ridge.

[b] The patient weighed only 47 kg (103 pounds).

[c] Papillary muscles only.

[d] Examined by gross inspection only (that is, by making multiple cross sections of the vessels [3 to 5 mm apart] in the intact specimen, and then viewing the arterial lumens grossly).

[e] Echocardiogram recorded 1 1/2 years before death showed asymmetric septal hypertrophy (ventricular septal thickness 18 mm, posterior left ventricular free wall thickness 13 mm and septal-free wall thickness ratio 1.4).

[f] Septal infarct was present predominantly in the region of the left ventricular apex.

[g] Extensive endocardial fibrosis, but not a typical discrete plaque.

+ = present; 0 = absent; ↑ = increased.

AL = anterolateral papillary muscle; AML = anterior mitral leaflet, LA = left atrium; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; LV = left ventricle; Max LVFW = maximal left ventricular free wall; pap = papillary muscles; Post LVFW = posterior left ventricular free wall (behind posterior mitral leaflet at the level of the inferior margins of mitral leaflets); PM = posteromedial papillary muscle; RA = right atrium; RCA = right coronary artery; RV = right ventricle; VS = ventricular septum.

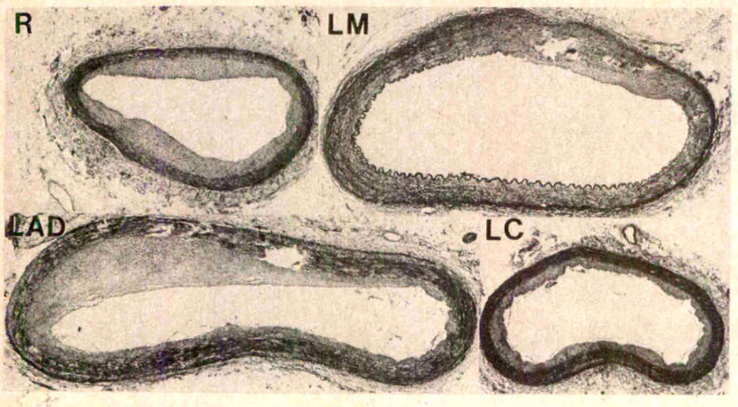


FIGURE 10. Case 2. Sections of the major extramural coronary arteries at sites of maximal narrowing. Each artery is free of significant narrowing (Movat stain ×16, reduced by 37 percent). LAD = left anterior descending, LC = left circumflex, LM = left main and R = right coronary artery, respectively.

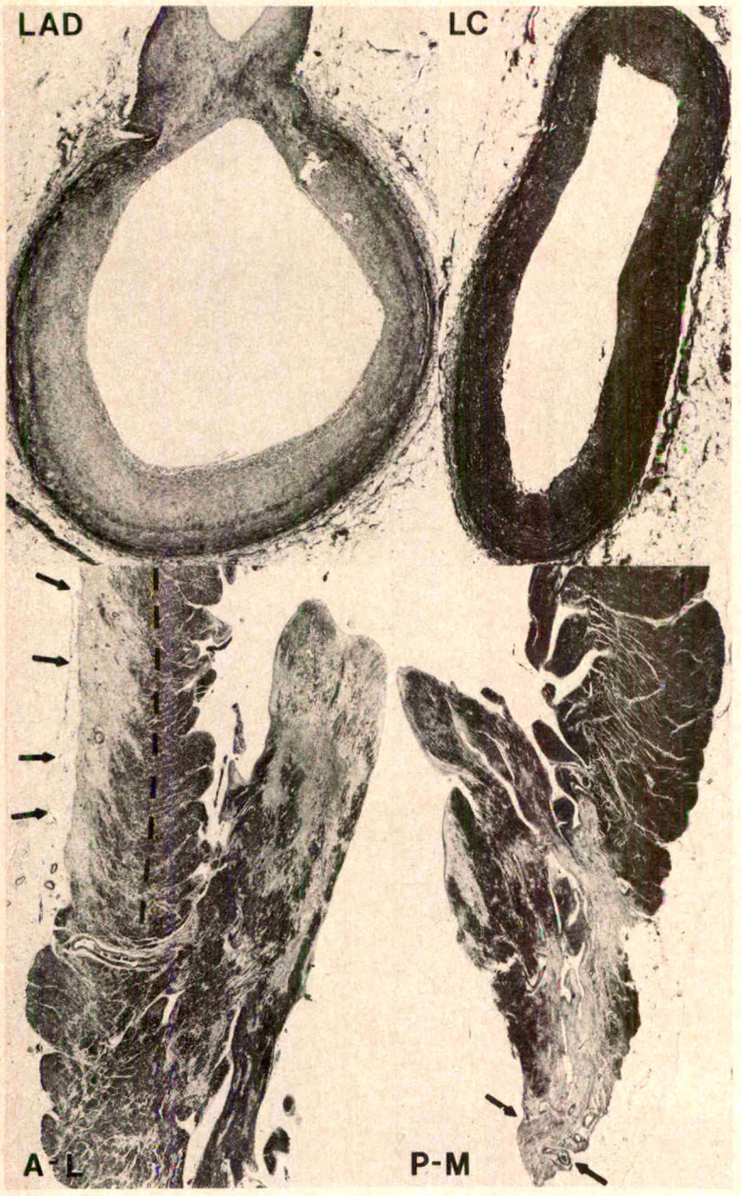


FIGURE 11. Case 7. Sections of the left anterior descending (LAD) and left circumflex (LC) coronary arteries (**top**) and of the left ventricular free wall and papillary muscles (**bottom**). Both coronary arteries are free of significant narrowing (Movat stains ×25, reduced by 20 percent). **Lower left,** section of left ventricular free wall and anterolateral papillary muscle (A-L); the scarring is localized to the subepicardial region of the left ventricular free wall (**arrows**) and to the distal half of the papillary muscle; the **broken line** serves to divide the inner from the outer halves of the ventricular wall (phosphotungstic acid-hematoxylin stain, ×3, reduced by 20 percent). **Lower right,** section of the left ventricular free wall and posteromedial papillary muscle (P-M) showing a transmural scar at the base of and caudal to the papillary muscle (**arrows**); focal scars also are present in the papillary muscle (phosphotungstic acid-hematoxylin stain ×3, reduced by 20 percent).

medial hypertrophy, or both) and narrowed lumens. Abnormal intramural coronary arteries were most common in the ventricular septum and in areas of scarring.

Myocardial infarcts: One or more foci of transmural left ventricular scarring (that is, replacement fibrosis) were present in each of the seven patients. One of these patients had an acute infarction manifested histologically by coagulation necrosis (loss of contractile elements, granularity of the cytoplasm and nuclear pyknosis or karyolysis) as well as healed myocardial infarcts (Fig. 12). The scars usually involved greater than 75 percent of the overall ventricular wall thickness.

Extensive transmural scars were present in the left ventricular free wall of six of the seven hearts (Fig. 2e, 3f, 8b, 9d, 10, 11 and 12, d and e). In each patient extensive scarring or necrosis of either one or both left ventricular papillary muscles was also evident (Fig. 11 and 12d). In addition, each of these patients had transmural scarring of the ventricular septum (Fig. 2d, 3e, 8c and 13).

The size of the left ventricular scars varied considerably. Three patients (Cases 2, 3 and 7) had particularly extensive transmural scarring involving the anterior, posterior, basal and apical regions of the left ventricular free wall and also contiguous areas of the ventricular septum. In contrast, Patient 5 (who had an occluding clot of the right coronary artery) had a relatively discrete transmural scar of the left ventricle that was limited to the posterobasal regions of the left ventricular free wall and septum (Fig. 12). The origin of the coronary clot in this patient, who also had pulmonary and renal infarcts due to emboli, is uncertain.

Four patients also had transmural scars involving the right ventricular wall (Fig. 8c). In three patients the scar was extensive and involved both the anterior and posterior right ventricular walls, and in the other patient (Case 1) the scar was relatively small and involved only a portion of the anterior right ventricular wall.

In addition to the transmural scars *subendocardial areas* often showed scarring (Fig. 13d). Three patients (Cases 3, 5 and 7) also had scarring in the *subepicardial* region of the basal left ventricular free wall (Fig. 9, a and b, 11, and 12f).

Discussion

Prevalence and clinical findings: Our study demonstrates that transmural myocardial infarction* may occur in patients with hypertrophic cardiomyopathy in the absence of significant atherosclerosis of the extramural coronary arteries. Furthermore, transmural infarction was present in 15 percent of our sizable group of nonsurgically treated patients who died of hypertrophic cardiomyopathy.

Transmural infarction was usually clinically "silent"; that is, it was accompanied by clinical manifestations of acute myocardial infarction in only one patient. Furthermore, the electrocardiogram was generally of little value in identifying the site of necrosis or fibrosis in our patients. Because 10 of 25 patients who did not have transmural infarction (or significant extramural coronary arterial narrowing) at necropsy also had electrocardiographic abnormalities (deep, wide Q waves) consistent with a healed myocardial infarct, the presence of such electrocardiographic changes was not reliably predictive of transmural scarring.

Clinical course: Six of our seven patients had a relatively unusual clinical course for patients with hypertrophic cardiomyopathy—that is, one characterized by supraventricular arrhythmias and profound progressive congestive heart failure with ventricular dilatation (documented with echocardiography and at necropsy). Two such patients (Cases 2 and 6) with marked congestive heart failure and a dilated poorly contractile left ventricle had shown a nondilated hypercontractile heart on angiography 8 and 9 years earlier in their clinical course. This evolution from a nondilated to a dilated left ventricle coincided with symptomatic deterioration in these patients. The clinical and morphologic features of such patients with "end-stage" hypertrophic cardiomyopathy have not been reported by previous investigators. However, in our experience and in that of Goodwin[35–37] and Oakley,[38] the clinical state of the large majority of patients with hypertrophic cardiomyopathy and chronic congestive heart failure does not usually evolve into one characterized by left ventricular dilatation.

Necropsy findings: Areas of the ventricular septum and left ventricular free wall involved by transmural infarction were particularly large in six of the seven patients. In four patients, portions of the right ventricular wall also were infarcted. The large infarcts in these patients usually occurred without clinical evidence of accompanying acute myocardial infarction. However, the extent of transmural infarcts in the left and right ventricular walls was not related to the age of the patient, nor did the regions of the left ventricle involved by infarcts generally correspond to any particular coronary arterial distribution (as noted, Patient 5 is an exception to this).

The extent of infarction in our patients with hypertrophic cardiomyopathy exceeded that usually present in patients with idiopathic dilated cardiomyopathy.[15–17] In the latter group of patients transmural infarcts are uncommon, relatively small and usually confined to the left ventricular free wall. Also, three of our seven patients with transmural myocardial infarction had nontransmural infarcts limited to the *subepicardium* of the basal left ventricular free wall. Although the significance of this peculiar location of myocardial scarring is uncertain, scarring in this region of the left ventricle is unique, and we have not observed it in patients with

* The term "myocardial infarct" (or "infarction") is used in this paper to describe extensive myocardial cell necrosis that has undergone healing (that is, shows extensive replacement fibrosis). Although coagulation necrosis was present in the heart of only one of our seven patients it is our presumption that necrosis must have preceded the *extensive* scarring (replacement fibrosis) identified in the other six patients.

coronary or valvular heart disease or dilated cardiomyopathy.

Left and right ventricular dilatation was present in six (86 percent) of our seven patients with hypertrophic cardiomyopathy and transmural infarction. In two patients the ventricular dilatation was marked, similar to that present in dilated cardiomyopathy.[15–17] In contrast, only four (10 percent) of our 41 nonsurgically treated necropsy patients with hypertrophic cardiomyopathy but without transmural myocardial infarction had ventricular dilatation ($P < 0.001$). Hence, transmural infarction appears to predispose to ventricular dilatation in patients with hypertrophic cardiomyopathy.

Mural thrombi (similar to those present in about 70 percent of patients with dilated cardiomyopathy[15–17]) occurred in four of our seven patients. Because ven-

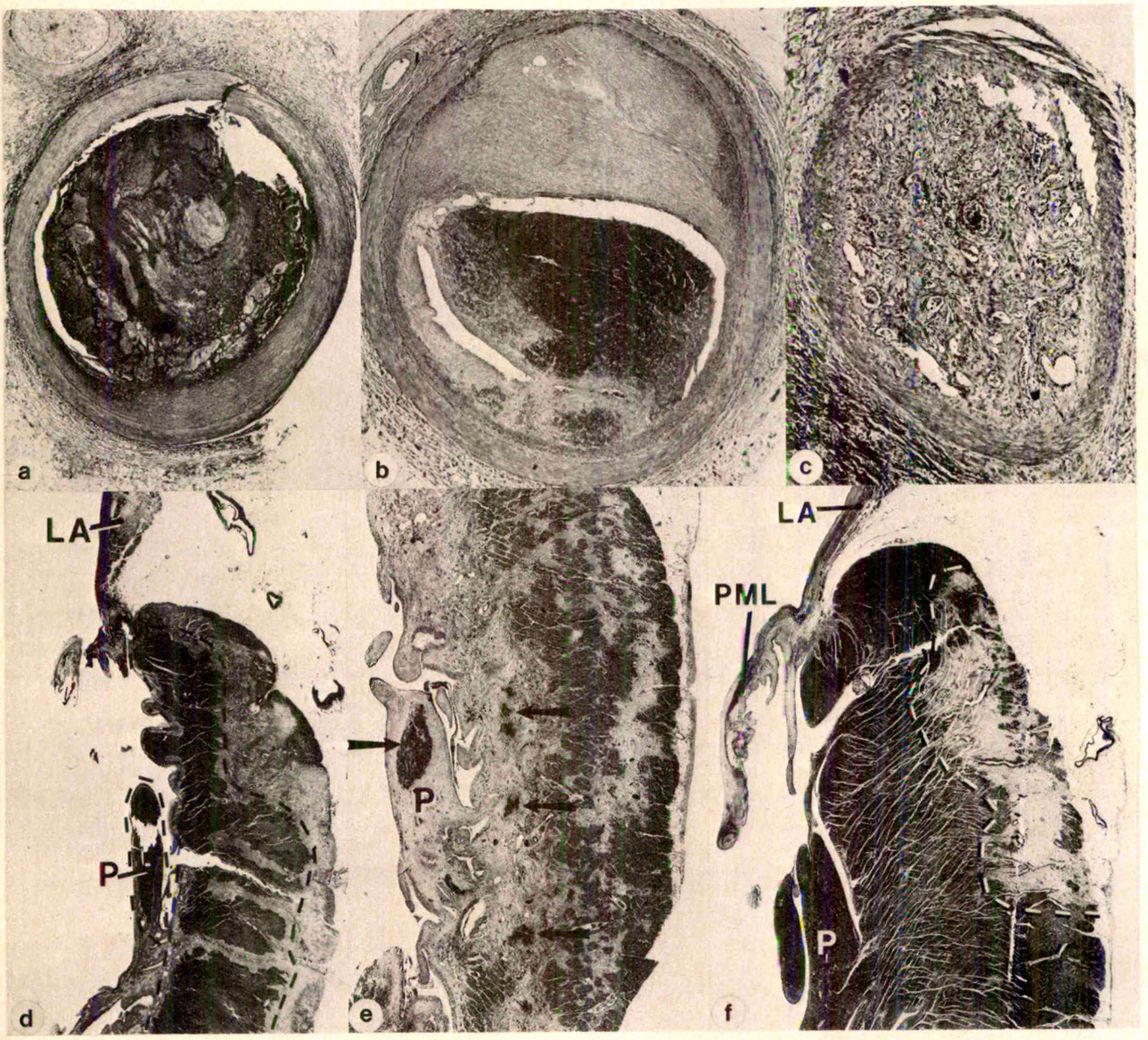


FIGURE 12. Case 5. Sections of the right coronary artery at three levels in the area of the embolus (**top**) and of the left ventricular wall (**bottom**). **a,** proximal portion containing clot (mainly fibrin), which is beginning to organize. The artery is nearly free of underlying atherosclerotic plaque, suggesting an embolic origin of the clot. **b,** same artery but just proximal to crux. Here the clot is clearly organizing and it fills less than half the residual lumen. The underlying plaque may have resulted from organization of the clot. **c,** small branch of the right coronary artery (posterior descending) in which the lumen is filled with loose fibrous tissue containing numerous channels. The presence of the multiple channels is evidence of organization of a clot. **d,** section of the posterior portion of the left ventricular (LV) wall and posteromedial papillary muscle (P) showing extensive necrosis (**dark areas within broken lines**), some of which is subendocardial only and other portions that are transmural. The papillary muscle is totally necrotic; LA = left atrium. **e,** another portion of the posterior left ventricular free wall with posteromedial papillary muscle (P) midway between base and apex. Here there is considerable fibrous scarring (light areas) with only small islands of necrosis (**arrows**). **f,** basal portion of the left ventricular free wall in another area showing only subepicardial scarring (light areas demarcated by broken line); PML = posterior mitral leaflet; LA = left atrium. **a, b,** and **c;** Movat stain ×16, 25 and 65, respectively, reduced by 20 percent; **d,** phosphotungstic acid-hematoxylin stain (×2.5, reduced by 20 percent); **e, f,** hematoxylin-eosin ×5, reduced by 20 percent.

tricular thrombi usually occur in the setting of markedly diminished cardiac output it is not surprising that they have not been observed in patients with hypertrophic cardiomyopathy and nondilated ventricles.

Etiology of transmural infarction: The etiology of transmural myocardial infarction in patients with hypertrophic cardiomyopathy and without significant coronary atherosclerosis is unclear. Several causes appear to be possible. *First, the cardiac mass may have been too great for the existent coronary blood supply and its capacity to deliver oxygen to the myocardium.* This possibility is suggested by the findings in Patient 3, who had a massive heart weighing 1,250 g (although the patient weighed only 47 kg). However, this explanation is untenable for the other six patients with transmural infarction because their heart weight did not exceed 580 gs. *Second, myocardial infarction could have been due to an occluding embolus of a major coronary artery,* which subsequently lysed.[39–42] In Patient 5 a partially organizing embolus (of unknown origin) was present in the right coronary artery. However, this patient had a relatively discrete transmural infarct of the ventricular septum and the posterobasal region of the left ventricular wall; hence, if an embolus to a single coronary artery had been responsible for infarction in any of the other study patients, the resultant areas of scarring would probably not have been as extensive as those observed. Although we cannot rule out the possibility that multiple, small coronary emboli were responsible for our findings, the lack of clinical evidence of systemic emboli elsewhere in the other six patients makes this hypothesis unlikely.

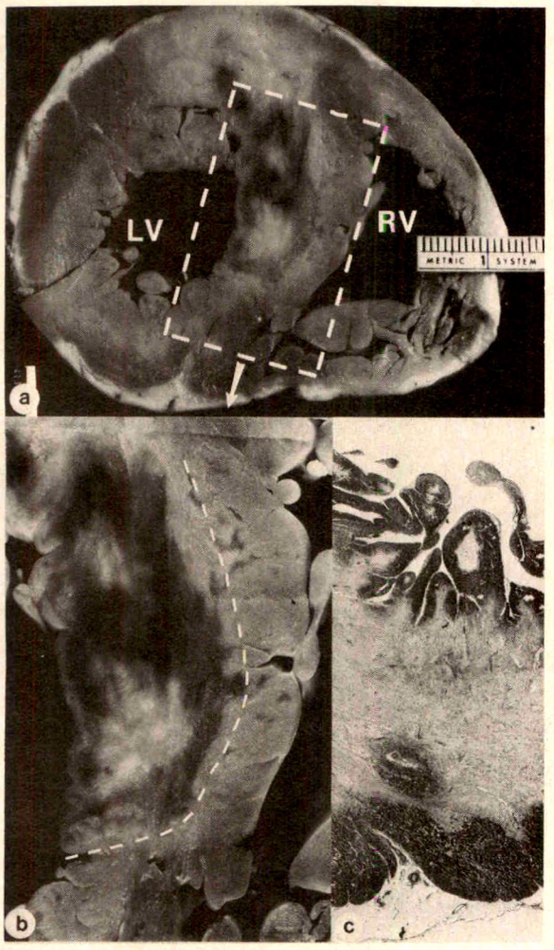


FIGURE 13. Case 1. Transmural myocardial fibrosis in ventricular septum. **a,** in a transversely cut section of the heart, an extensive septal infarct is demarcated by the **broken line;** LV and RV = left and right ventricle, respectively. **b,** area of infarction (outlined by **broken line**) shown at higher magnification. **c,** histologic section of the transmural infarct showing extensive replacement fibrosis; taken from area shown in **a** and **b** (phosphotungstic acid-hematoxylin ×3, reduced by 35 percent).

Third, it is possible that infarction in our patients was related, at least in part, to narrowing of the intramural coronary arteries. Particularly marked thickening of the walls and narrowing of the lumens of numerous intramural coronary arteries was present in the left ventricular myocardium in six of the seven patients with transmural infarction. Although abnormalities of the intramural coronary arteries have been reported in a wide variety of cardiac or systemic diseases,[43] the arterial alterations identified in the patients with hypertrophic cardiomyopathy and transmural infarction constitute, in our experience, the most widespread and marked example of "small vessel disease." Nevertheless, because abnormal intramural coronary arteries were not present in one of our patients with transmural myocardial infarction, the causal relation between these two abnormalities cannot be considered definitive. *Fourth, recent studies have shown that myocardial infarction may be precipitated by coronary spasm in vessels either with or without atherosclerotic plaques.*[44–48] Although it is possible that vasospasm (of either the extramural or abnormal intramural coronary arteries) was responsible for myocardial infarction in our patients with hypertrophic cardiomyopathy and "normal" extramural coronary arteries, we cannot be definitive about such a mechanism.

Finally, brief periods of hypoxia or hypotension might have been responsible for the transmural myocardial scarring observed in certain of our patients. For example, in Patient 1 it is most likely that the myocardial infarction either preceded or caused the cardiac arrest (based on a histologic assessment of the age of the infarct). However, we cannot definitively exclude the possibilities that the patient had a cardiac arrest due to a primary arrhythmia and that the infarct was a consequence of hypoxia or resuscitative efforts, or both, at the time of arrest. Ten weeks before death, Patient 7 had a severe episode of bradycardia associated with hypotension. However, it seems unlikely that the extensive myocardial scarring in this patient could have been due to this relatively brief period of hypotension.

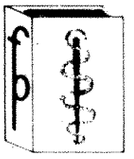
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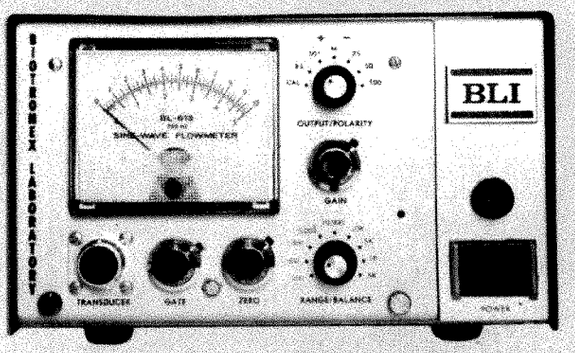
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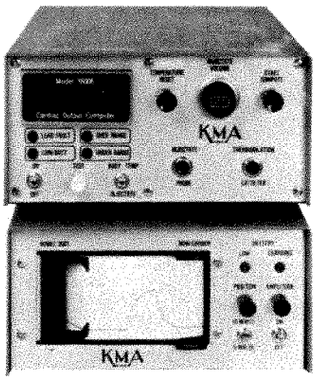
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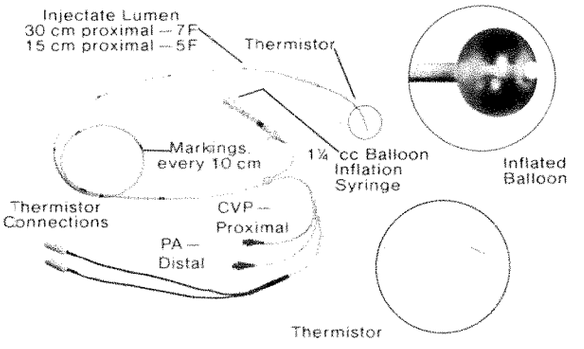
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- AUTOMATIC thermal curve recording
- CHOICE of injectate volume and temperature
- SERVICEABLE — interchangeable circuitry

THERMODILUTION CATHETERS



Features:

- Convenient and complete sterile packaging
- Precalibrated and interchangeable
- Adult, pediatric and direct placement sizes
- Tapered tip — pressure fidelity and introduction
- Thermistor located inside J curve — prevents P.A. wall contact
- Balloon protection shield

KMA INC

For additional information contact Ross A. Linnemann

KIMRAY MEDICAL ASSOCIATES

53 N.W. 42nd, Oklahoma City, Oklahoma 73118

(405) 525-3823

An antihypertensive that's easy to live with



...for them, and for you.

Lopressor™
metoprolol tartrate

...the relatively selective beta blocker for hypertension.

Does not interfere with sex life of patients.

Lopressor usually does not cause impotence or loss of libido, complaints which many male patients encounter with sympathetic inhibitors, but which they may be reluctant to discuss with their physicians.

Rarely causes daytime sedation or postural hypotension.

Most of the side effects that have occurred with Lopressor are mild and transient. For example, tiredness and dizziness occur in about 10% of patients; depression, diarrhea in about 5%. Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt heart failure.

Easy to take twice-a-day dosage.

Patients will also appreciate the easy-to-remember b.i.d. dosage of Lopressor. Since b.i.d. dosage is known to encourage patient adherence, this is another way that Lopressor improves your chances for long-term therapeutic success.

Significantly reduces blood pressure when added to a diuretic.

Lopressor caused a significant fall in blood pressure when given to patients already receiving a diuretic. Investigators reporting in the British Journal of Pharmacology concluded that "Metoprolol in combination with chlorthalidone appears to be an effective and well-tolerated treatment for mild and moderate hypertension in those patients not responding to chlorthalidone alone."*

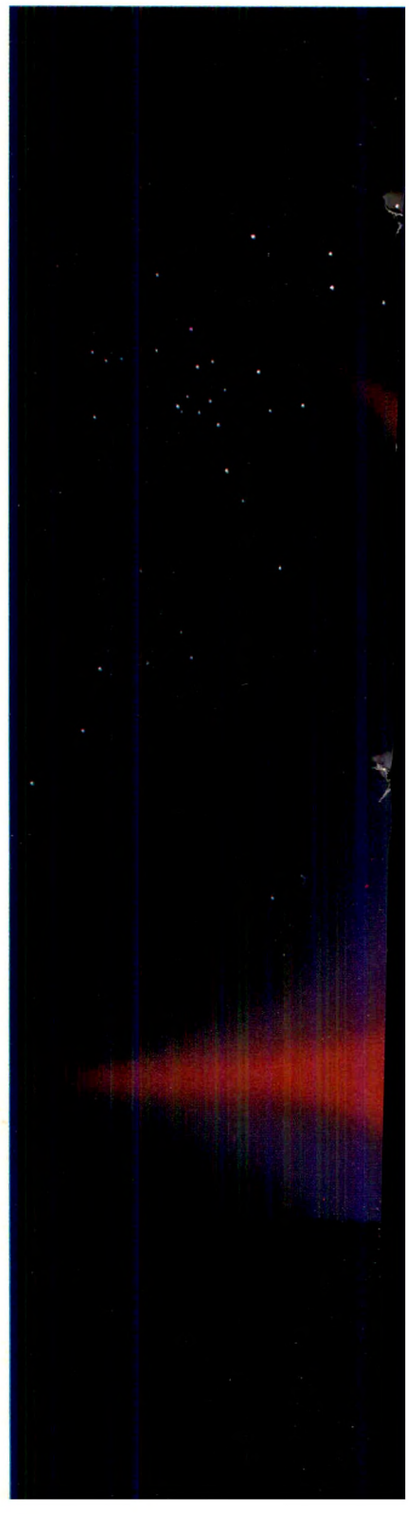
Treatment Period		
Placebo + chlorthalidone		**Metoprolol + chlorthalidone**
one month		
	Systolic BP (mmHg)	
158±4	supine	142±4
160±5	standing	147±3
	Diastolic BP (mmHg)	
96±2	supine	87±1
102±2	standing	94±1
two months		
	Systolic BP (mmHg)	
159±4	supine	146±4
159±4	standing	147±4
	Diastolic BP (mmHg)	
96±2	supine	89±1
101±2	standing	95±1
three months		
	Systolic BP (mmHg)	
158±5	supine	148±3
159±4	standing	149±3
	Diastolic BP (mmHg)	
97±2	supine	87±1
101±2	standing	93±1

Works primarily where it should... not where it shouldn't.

Lopressor is the only relatively selective beta blocker available in the United States. Unlike the first generation beta blocker, propranolol, which is nonselective, Lopressor has a preferential effect on beta receptors involved in lowering blood pressure. It has less effect on beta receptors that do not relate to antihypertensive mechanisms.

Please see last page of this advertisement for brief summary of prescribing information.

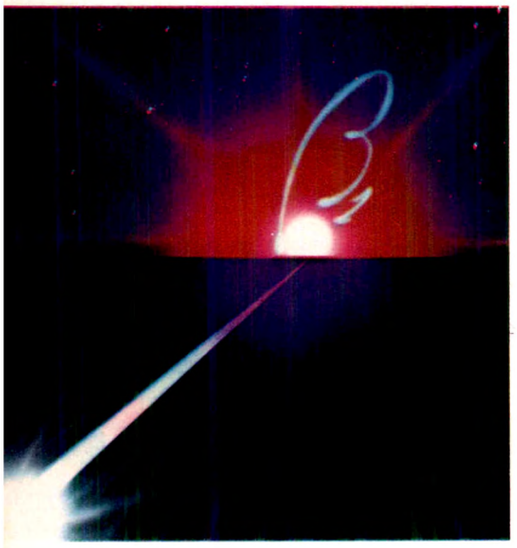
*Jäättelä A, Pyörälä K: A controlled study on the antihypertensive effect of a new β-adrenergic receptor blocking drug, metoprolol, in combination with chlorthalidone. Br J Pharmacol 3:655-660, 1976.





The relatively selective beta blocker for hypertension.

Lopressor™
metoprolol tartrate



Lopressor™
brand of metoprolol tartrate

An antihypertensive beta-blocking agent

Indications Lopressor, brand of metoprolol tartrate, is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor, brand of metoprolol tartrate, is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor, brand of metoprolol tartrate, should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor, brand of metoprolol tartrate, therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor, brand of metoprolol tartrate, should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor, brand of metoprolol tartrate, may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in three doses daily, instead of two, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor, brand of metoprolol tartrate, should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor, brand of metoprolol tartrate, plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor, brand of metoprolol tartrate, should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, Raynaud's disease, palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor, brand of metoprolol tartrate, during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor, brand of metoprolol tartrate, should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor, brand of metoprolol tartrate, is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

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Before prescribing or administering, please consult complete product information.

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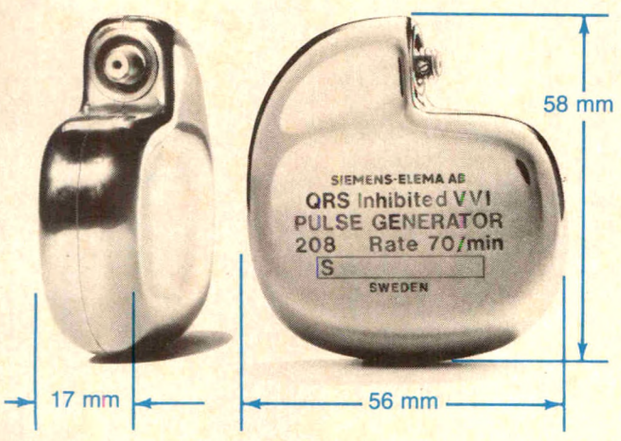
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Two new Lithium Pulse Generators from Siemens-Elema, the people who pioneered with the first implanted pacemaker in 1958.

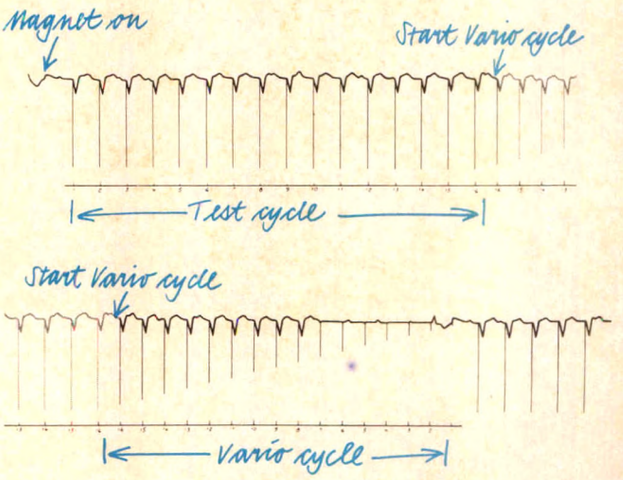
Dr. Rune Elmqvist of Siemens-Elema and Dr. Ake Senning developed the pulse generator implanted by Dr. Senning in 1958 for the world's first pacemaker implantation.

The small, lightweight, anatomically contoured, ventricular inhibited **208**.



- **Small (36 cm³) and lightweight (76 g.).**
- **Soft, convex-concave design.**
- **Hermetically sealed titanium encapsulation.**
- **Highly reliable hybrid circuitry.**
- **Lithium-Iodine power source.**
- **Two separate battery depletion indicators.**
- **Tangential lead connection.**

The unique Vario® non-invasive threshold measurement system in the ventricular inhibited **629**.



- **Magnet placed over implanted generator initiates test sequence:**
  Battery test cycle (phase 1).
  Vario cycle (phase 2) for threshold determination.
- **Compatible pin-type leads.**
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- **Lithium-Iodine power source.**
- **Two separate battery depletion indicators.**

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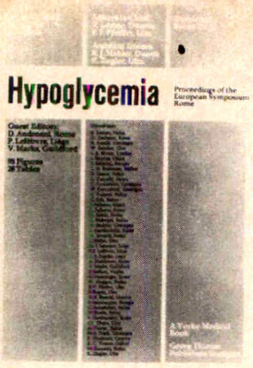
WRITE FOR 208 BROCHURE

SIEMENS-ELEMA

U.S. Pacemaker Division, Elema-Schonander, Inc.
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World Headquarters, Pacemaker Division, S17195, Solna, Sweden



WRITE FOR 629 BROCHURE



One of the Most Frequently Overdiagnosed Diseases!

■ *Here at last is an objective study of essential reactive hypoglycemia . . . definition, recognition, pathology, etiology, and treatment.*

Editors:

D. Andreani, MD, Prof. of Clinical Endocrinology, Univ. of Rome
P. Lefèbvre, MD, Dept. of Medicine, University of Liège
V. Marks, DM, Prof., Dept. of Biochemistry, Univ. of Surrey

This European (Rome) Symposium was the first free interchange of ideas among scientists in the various medical disciplines—physiology, internal medicine, endocrinology, clinical biochemistry, etc.—necessary to the understanding, diagnosis and treatment of hypoglycemia. The concentration was on the various aspects of insulin-producing tumors and the vexed question of essential reactive hypoglycemia. Special attention was given to the widespread misinterpretation of laboratory data relating to the prolonged oral glucose test which has resulted in the erroneous belief that "millions suffer from hypoglycemia."

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FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.

The following infections usually respond to adequate dosage of IM penicillin G benzathine.

Streptococcal infections (Group A—without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).

Venereal infections — Syphilis, yaws, bejel, and pinta.

Medical conditions in which penicillin G benzathine therapy is indicated as prophylaxis:

Rheumatic fever and/or chorea — Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures if superinfection occurs.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Composition: (units penicillin G benzathine as active ingredient in aqueous suspension): 300,000 units per ml—10-ml multi-dose vial. Each ml also contains sodium citrate buffer, approximately 6 mg lecithin, 3 mg povidone, 1 mg carboxymethylcellulose, 0.5 mg sorbitan monopalmitate, 0.5 mg polyoxyethylene sorbitan monopalmitate, 1.2 mg methylparaben and 0.14 mg propylparaben.

600,000 units in 1-ml TUBEX® (sterile cartridge-needle unit) Wyeth, packages of 10.

900,000 units, 1.5-ml fill in 2-ml TUBEX, packages of 10.

1,200,000 units in 2-ml TUBEX, packages of 10, and in 2-ml single-dose disposable syringe, packages of 10.

2,400,000 units in 4-ml single-dose disposable syringe, packages of 10.

Each TUBEX or disposable syringe also contains sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben and 0.01% propylparaben.

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INJECTION
BICILLIN® L-A
(STERILE PENICILLIN G BENZATHINE SUSPENSION)

Wyeth Laboratories
Philadelphia, Pa. 19101



GUESS WHAT PROTECTION HE'LL FORGET TO TAKE.

For rheumatic fever prophylaxis he can't forget:

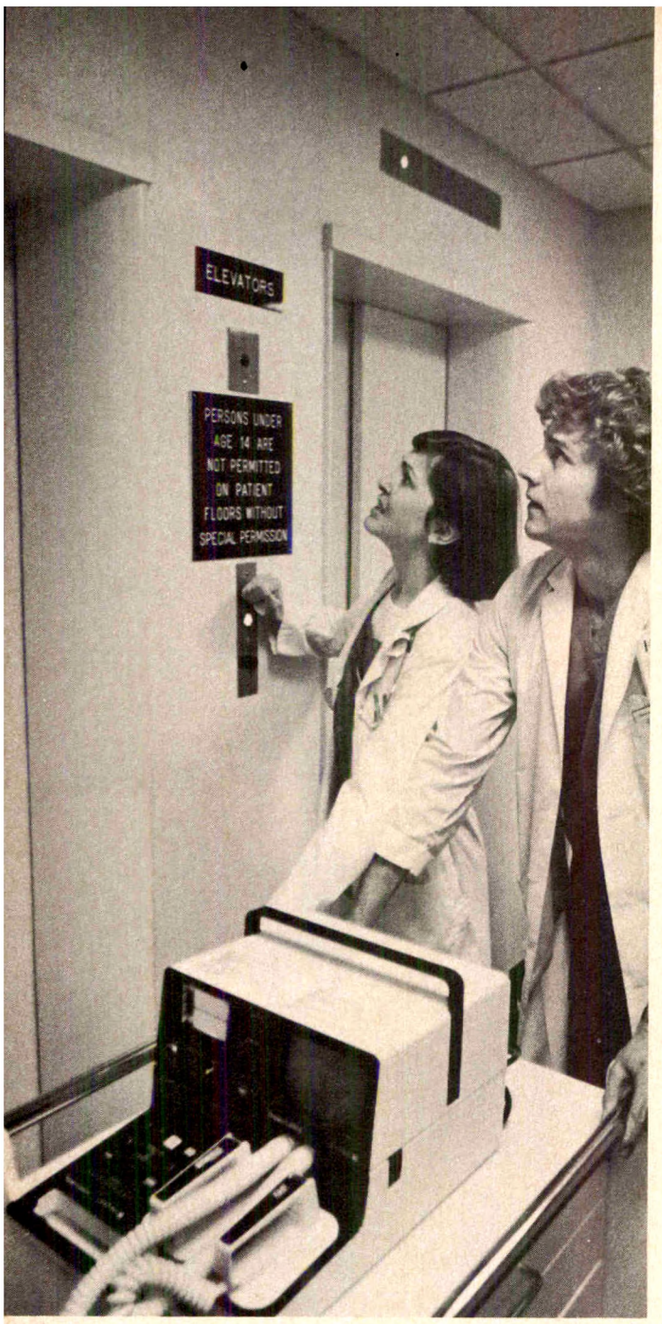
Injection penicillin G benzathine is the recommended drug of choice* to prevent streptococcal infection and possible recurrence of rheumatic fever. One injection, once a month, of 1,200,000 units usually offers effective and continuous prophylaxis, virtually eliminating the problem of patient compliance.

*Commission on Rheumatic Fever and Bacterial Endocarditis of the Council on Cardiovascular Disease in the Young: "Rheumatic Fever Prevention," 71-006-B. American Heart Association, New York, (Sept.) 1976.

INJECTION
BICILLIN® L-A
(STERILE PENICILLIN G BENZATHINE SUSPENSION)

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◀ See important information on preceding page.



Why your hospital needs a defibrillator on every floor.

All hospital elevators are notoriously slow. And with good reason, because in a hospital, the elevators are really freight elevators to move people and patients, equipment and supplies.

But when a life is ticking away, you can't afford to be waiting for the elevator. Will it come straight down? Or will it stop on another floor to pick up a patient on a gurney or to move on a food cart or to pick up linen or to transport visitors? Who knows? All you *really* know is that a life is ticking away and you're waiting for the elevator.

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(isosorbide dinitrate)

HELPS THE HEART IN THE CONTROL OF ANGINA PECTORIS*

The established use of Isordil in the management of angina pectoris for more than two decades has often been ascribed only to the vasodilatation it produces in the coronary arteries. Recent investigations, however, suggest that an even more important effect of this agent is to dilate peripheral arteries and veins. Arterial dilatation lowers impedance to left ventricular ejection, reducing afterload. Venous dilatation leads to venous pooling and a fall in right and left ventricular filling pressure, thus reducing preload.

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to abort or prevent acute angina attacks

ISORDIL® SUBLINGUAL
Sublingual Tablets, 2.5 mg and 5 mg

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Chewable Tablets, 10 mg

for more accurate titration of dosage to prevent angina attacks

ISORDIL® TITRADOSE®†
Oral Tablets with E.Z. Split® scoring:
5 mg, 10 mg, and 20 mg

to provide sustained prophylaxis against angina

ISORDIL® TEMBIDS® Capsules
Sustained-Action Capsules, 40 mg

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

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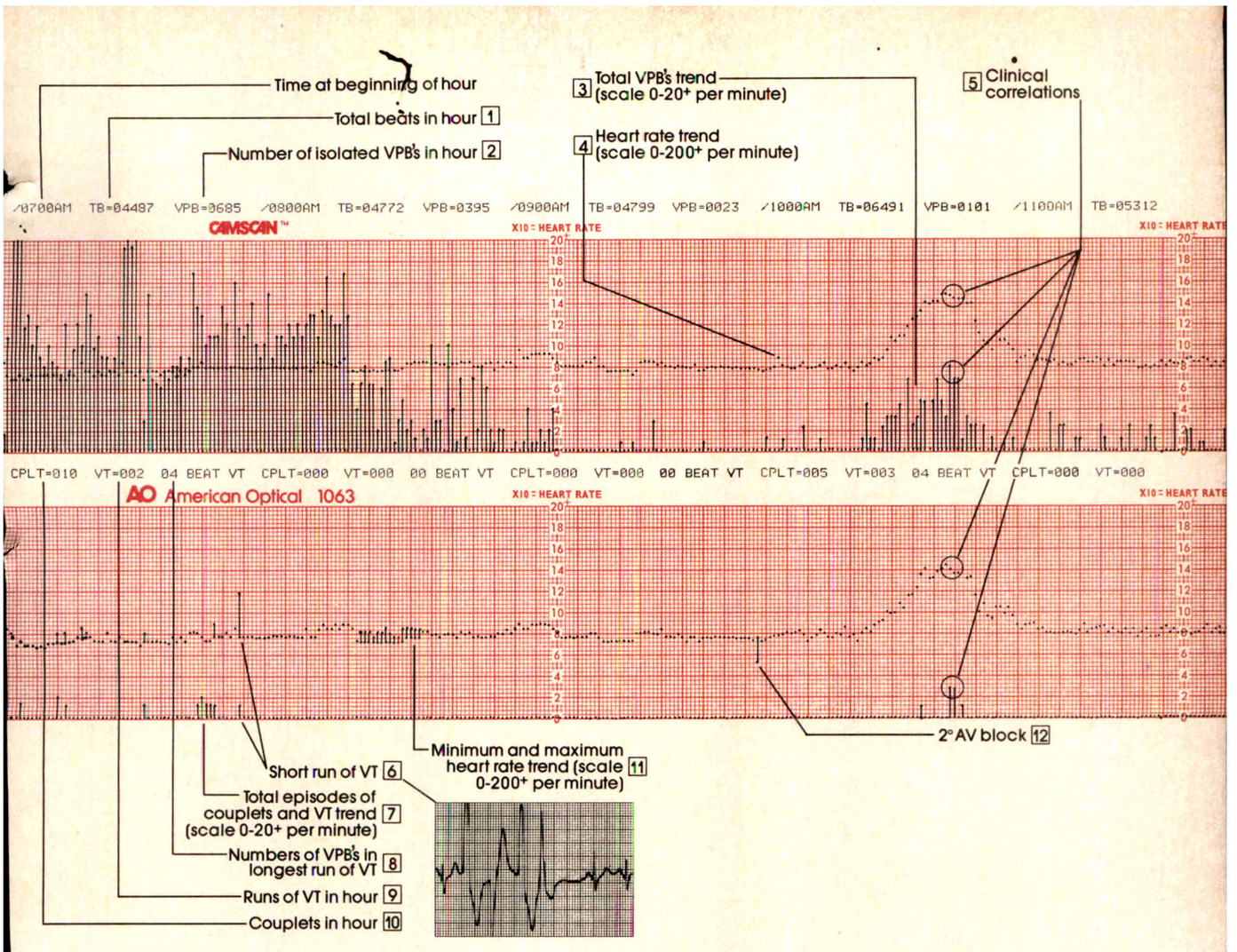
The New CAMSCAN™ System

accurate, verifiable, clinically valuable Holter information.

- ☐ an informative, intuitive arrhythmia report, indexed to the minute, the central element in your scanning report, serves also as a roadmap to reduce the time required for the manual scan.
- ☐ each CAMSCAN System Arrhythmia Report is verifiable through two independent means:

  first verification: take advantage of the to-the-minute accuracy of the system and rapidly examine two or three places on the tape corresponding to periods of high activity on the CAMSCAN System Report.

  second verification: during the documentation (manual) scan, program three audible tones to sound whenever various arrhythmias are detected—perform an audio vs visual check for false classifications.



A better way to report cardiac events: The CAMSCAN System Arrhythmia Report.

- ☐ trends number of heartbeats in each minute (4).
- ☐ trends minimum and maximum heart rate in each minute (11), thereby highlighting sinus pauses and blocks (12) that an operator may miss.
- ☐ counts and prints number of heartbeats in each hour (1).
- ☐ trends total VPB's (3) as well as episodes of couplets and V-tach (7) in each minute.
- ☐ counts and prints isolated VPB's (2), couplets (10), and runs of V-tach (9) in each hour in accordance with commonly used arrhythmia classifications.
- ☐ counts and prints number of VPB's in longest run of V-tach (8).
- ☐ shows short runs of V-tach usually as increased maximum heart rate (6).
- ☐ shows clearly relationships between heart rate and ventricular ectopic activity, both with respect to each other and with respect to time (5). Heart rate and ectopic events can then also be easily correlated with event marks and the patient's activities, symptoms, and medications.
- ☐ summarizes data from a 24-hour CAMSCAN System tape in just 13 minutes of unattended scan.

To get more information on what the unique features and benefits of the CAMSCAN System can mean in your practice, contact your local AO representative.

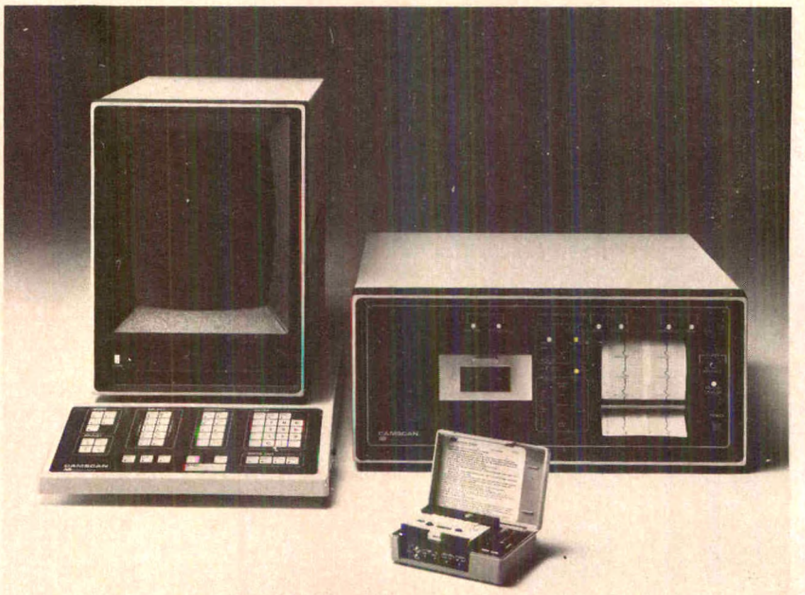
The New CAMSCAN System

...clearly defined Holter monitoring benefits

AO American Optical MEDICAL DIVISION
Crosby Drive, Bedford, MA 01730

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Occlusive Disease Confined to the Right Coronary Artery: Clinical Features, Surgical Treatment and Long-Term Follow-Up in 124 Patients

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The clinical presentation and surgical results in 124 consecutive patients who underwent aorta to right coronary arterial bypass surgery from January 1970 through June 1977 were reviewed. Preoperatively, 75 percent of the patients were in New York Heart Association functional class III or IV, 9 percent presented with unstable angina and 5 percent had life-threatening ventricular arrhythmias. All patients had high grade occlusive disease confined to the right coronary artery; 34 percent of the patients had associated nonsignificant disease (less than 50 percent intraluminal narrowing) of the left anterior descending or circumflex artery. Left ventricular function was normal in 63 percent and minimally impaired in 37 percent. The operative mortality rate was 1.6 percent. The course of the 122 survivors was followed up for 3.7 years. There were four late deaths, and the 5 year mortality rate was 4.0 percent. Eight patients were reoperated on because of recurrence of symptoms and occlusion of the graft or progression of occlusive disease of the other major coronary arteries, or both. Of the remaining 110 patients, 98 are either in functional class I or II, 60 are taking no cardiovascular medications, 52 are working full time without angina and 73 are asymptomatic. In summary, bypass surgery for isolated right coronary artery disease has a low mortality rate and results in excellent long-term symptomatic improvement.

Myocardial revascularization using aortocoronary saphenous vein bypass grafts for patients with coronary arterial occlusive disease has been enthusiastically accepted because the procedure results in a high rate of symptomatic relief and in low surgical mortality rate.[1–4] Although studies on the natural history of coronary atherosclerotic disease using coronary arteriography[5–9] have defined subsets of patients who are at various degrees of risk of death, data are still inadequate on both the clinical course of patients with significant obstructive lesions confined to the right coronary artery[7,9] and the effects of bypass surgery on their long-term survival. Only the long-term results of double blind, randomized studies comparing the bypass procedure with standard medical therapy will ultimately establish its value as a treatment for isolated obstructive disease of the right coronary artery.[10–13] As an interim measure we critically analyzed the clinical presentation and the surgical results in 124 consecutive patients who underwent aorta to right coronary bypass surgery.

Methods

Patients: One hundred twenty-four patients underwent saphenous vein bypass grafting of the right coronary artery in this institution as an isolated procedure between January 1970 and June 1977. Ninety-six patients were men and 28 were women. The mean age was 53 years (range 25 to 69). The age and sex distribution of the patients are shown in Figure 1. All had a high grade occlusive

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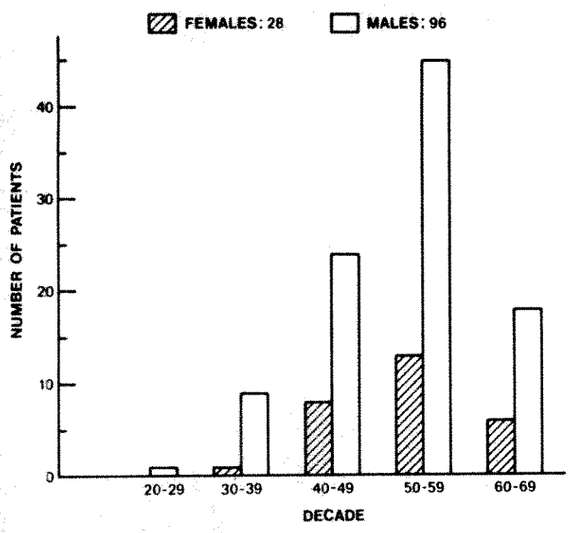


FIGURE 1. Age and sex distribution by decade in 124 patients with occlusive disease confined to the right coronary artery.

lesion (greater than 75 percent narrowing of the intraluminal diameter or total occlusion) confined to the proximal or mid portion of the right coronary artery and insignificant (less than 50 percent narrowing) occlusive disease of the left anterior descending or the left circumflex artery, or both. Patients undergoing right coronary bypass were excluded if they had prior revascularization procedures or had congenital heart disease, a surgically resectable ventricular aneurysm or valvular heart disease (other than mitral insufficiency thought to be secondary to ischemic heart disease). The selection of patients for bypass graft surgery was based on severity of symptoms, anatomic severity of the coronary lesions, the apparent integrity of the myocardium in the region perfused by the right coronary artery as well as, in part, the preference of the patient and his attending cardiologist. No attempts were made to assess the effectiveness of medical therapy in a particular patient.

Follow-up: Follow-up information concerning angina pectoris, myocardial infarction, functional classification, exercise stress test results and survival was obtained from the hospital charts and by telephone calls to the physician, the patient or his or her family. Three patients were lost to the postoperative follow-up studies, two after 1 year and one after 2 years; with inclusion of these patients the mean follow-up time was 3.7 years (range 1.0 to 7.5) after operation. All patients had a standard 12 lead electrocardiogram taken within a few days before operation and serial tracings after operation beginning with one taken immediately on arrival in the recovery room. Electrocardiographic evidence of previous myocardial infarction and the occurrence of a perioperative myocardial infarction were assessed using the criteria of the Minnesota Code.[14]

Angiography: Most of the coronary angiograms were performed according to the Judkins technique, although a small number were obtained using the Sones method. Angiographic estimate of degree of stenosis was based on decrease in diameter as judged in two projections to estimate reductions in lumen in terms of loss of cross-sectional area.[15] Stenoses of 75 percent or more were further subdivided into the following categories: 75 percent or more to less than 90%, 90 percent or more to less than 100 percent and 100 percent obstruction. Left ventriculograms performed in the 30° right anterior oblique projection were available for analysis in 110 (90 percent) of the cases. Ventricular function was evaluated on the basis of ejection fraction, according to the method of Sandler and Dodge,[16] cardiac size, contraction abnormalities and left ventricular end-diastolic pressure. Abnormal left ventricular function was defined as the presence of at least one of the following: (1) an ejection fraction of less than 50 percent, (2) one or more contraction abnormalities as demonstrated by any akinetic, hypokinetic or dyskinetic ventricular segment, (3) enlarged cardiac size on angiography as judged subjectively, or (4) left ventricular end-diastolic pressure greater than 14 mm Hg at rest.

Surgery: Cardiopulmonary bypass was employed in 109 of 124 patients. In the majority, aortic cross-clamping was not utilized. In 18 patients a right coronary endarterectomy was performed before bypass grafting. In 15 patients right coronary arterial bypass was performed without cardiopulmonary bypass.

Before and after operation all patients were given broad spectrum antibiotic therapy. The majority of patients received sodium warfarin from the 3rd day after the operation and continued to receive it for several months after operation. The

TABLE I

Preoperative Variables Relative to Patient's History

	Patients	
	no.	%
Duration of angina (mo)		
0–5	33	27
6–12	29	23
13–24	21	17
25–60	21	17
>60	20	16
Unstable angina	11	9
History of previous MI	42	34
NYHA functional class		
I	3	2
II	28	23
III	47	38
IV	46	37
History of hypertension	37	30
History of diabetes	14	11
History of CVD	3	2
History of PVD	23	18
History of increased serum cholesterol	21	17
History of cigarette smoking	93	75
Family history of CHD	69	56

CHD = coronary heart disease; CVD = cerebral vascular disease; MI = myocardial infarction; NYHA = New York Heart Association; PVD = peripheral vascular disease.

TABLE II

Extent of Electrocardiographic Abnormalities in 124 Patients

	Patients	
	no.	%
Normal	53	44
Inferior or posterior infarction	30	24
Resting ST-T wave abnormalities	26	21
Left axis deviation	6	5
Left ventricular hypertrophy	4	3
Ventricular conduction defects	3	2
Ventricular tachyarrhythmias	6	5
Ventricular tachycardia	4	...
Ventricular fibrillation	2	...

average duration of the hospital stay was 12 days (range 7 to 55).

We calculated the cumulative survival rates using the actuarial life-table method of Cutler and Ederer.[17]

Results

Clinical and Angiographic Baseline Features

The distribution of several variables relating to the patients' past history is displayed in Table I. Fifty percent of the patients had had angina for 1 year or less; 9 percent presented with unstable angina and 75 percent were classified as belonging to functional class III or IV of the New York Heart Association.[18] Of the three patients in functional class I, one had had a cardiac arrest 6 months before operation. The second patient had been hospitalized twice in the preceding 24 months because of severe myocardial ischemia and was treated with digitalis and propranolol. The third patient was a 41 year old man with a family history of sudden coronary death who had an episode of angina 1 month before operation. Cardiac catheterization and coronary arteriography demonstrated normal left ventricular function and an isolated 80 percent proximal stenosis of the right coronary artery. Previous coronary arteriograms in this patient, obtained at age 37 years while he was completely asymptomatic, had revealed a 30 percent proximal stenosis of the right coronary artery.

Of 93 patients in functional classes III and IV at the time of hospitalization for surgery, 65 patients (70 percent) were receiving long-acting nitrates or propranolol (44 and 41 patients, respectively) in addition to sublingual nitroglycerin. Of 37 patients with a history of hypertension, 10 (27 percent) were receiving antihypertensive medication and of 21 patients with a history of increased serum cholesterol, 11 (52 percent) were receiving clofibrate.

The extent of electrocardiographic abnormalities is summarized in Table II. Of six patients (5 percent) who had major ventricular tachyarrhythmias, three required direct current cardioversion. An exercise stress test (Master two step or treadmill stress test) was performed preoperatively in 52 patients; in 37 (71 percent) the test was reported as positive (1 mm or more S-T depression); in 14 patients it was negative.

The ventriculographic baseline findings (Table III) indicate that 41 patients had some left ventricular abnormality; 1 of these patients was in functional class I, 12 patients were in class II, 17 in class III and 14 in class IV. The severity of occlusive disease of the right coronary artery and the presence of disease in other vessels are shown in Table IV.

Survival Analysis

There were two perioperative deaths (within 30 days of surgery), both secondary to a myocardial infarction, resulting in a mortality rate of 1.6 percent. In both cases the patient was in functional class IV. One patient was a 44 year old woman who presented with unstable angina; she had a history of diffuse atherosclerotic vascular disease that included left carotid arterial stenosis and bilateral subclavian steal syndrome. A left carotid endarterectomy had been performed 1 month before cardiac surgery. Significant postoperative complications occurred in 16 patients, including nonfatal myocardial infarction (4 patients), sternal dehiscence (4 patients) and postcardiotomy syndrome (3 patients). Myocardial infarction was the leading cause of postoperative morbidity and had an incidence rate of 5 percent with inclusion of the two fatal myocardial infarctions noted earlier.

There were four late deaths. In one patient who died suddenly 8 months postoperatively, postmortem examination was not carried out. Two other patients died 11 and 21 months, respectively, after operation, the first of a cerebral vascular accident secondary to malignant hypertension and the second of carcinoma of the lungs. The last patient died 6 years postoperatively of an acute myocardial infarction during cholecystectomy. Cardiac catheterization performed 1 year earlier because of re-

TABLE III

Ventriculographic Baseline Variables in 110 Patients

	Patients	
	no.	%
LV function		
Normal	69	63
Abnormal	41	37
LV size		
Normal	98	89
Enlarged	12	11
LV contraction abnormalities	32	29
LV ejection fraction (%)		
>65	92	84
50 to 64	14	13
<50	4	4
LV end-diastolic pressure (mm Hg)		
0–14	92	84
>14	18	16
Mitral regurgitation	7	6

* Ejection fraction was calculated in 110 patients.
LV = left ventricular.

TABLE IV

Severity of Occlusive Disease of the Right Coronary Artery and Disease of Other Vessels in 124 Patients

	Patients	
	no.	%
Disease of right coronary artery		
75% to 89% stenosis	32	26
90% to 99% stenosis	59	47
Total occlusion	33	27
Collateral vessels	62	50
Dominant*	120	97
Balanced†	4	3
Disease in other vessels		
<50% stenosis of LAD	22	18
<50% stenosis of LCx	13	10
<50% stenosis of LAD and LCx	7	6

* Posterior descending coronary arteries originating from the right coronary artery.
† Posterior descending coronary arteries originating from the right coronary and left circumflex coronary arteries.
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

currence of symptoms had revealed severe triple vessel disease and an occluded bypass graft to the right coronary artery.

Postoperative clinical outcome in 118 survivors at the time of latest follow up (Table V): Excluding 8 patients who were reoperated on, 98 patients (85 percent) were either in functional class I or II; of these, 68 had been in either class III or IV preoperatively. Thirty-seven of 41 patients with preoperative left ventricular dysfunction and all 7 patients with mild mitral regurgitation were in functional class I or II postoperatively. Sixty patients (54 percent) were receiving no cardiovascular medication, 9 (8 percent) were receiving sublingual nitroglycerin, 19 (17 percent) long-acting nitrates, 25 (23 percent) propranolol, 7 (6 percent) antiarrhythmic medications, 11 (10 percent) antihypertensive medications and 10 (9 percent) clofibrate. All six patients with major ventricular tachyarrhythmias preoperatively were alive and receiving no antiarrhythmic medications.

Coronary arteriography was performed postoperatively in 18 patients (mean 24 months, after operation; range 3 to 59) because of recurrence of symptoms. A stenotic or occluded graft was found in 13 (72 percent) of this subgroup. Eight of the 18 patients had had significant progression (75 percent or greater luminal narrowing) of atherosclerotic occlusive disease of the left anterior descending or left circumflex artery, or both. Four patients received a second single vein bypass graft to the right coronary artery, two had double vein bypass grafts, one triple vein bypass grafts and one a single vein bypass graft to the left anterior descending coronary artery.

Exercise stress tests were obtained in 32 patients during the follow-up period; they were positive in 7 patients and negative in 25. Eleven of 18 patients with a positive test before operation had a negative test postoperatively.

TABLE V

Postoperative Clinical Outcome in 118 Patients

	Patients (no.)
NYHA classification*	
I	73
II	25
III	11
IV	1
Postoperative coronary arteriography	18
Stenosed graft	2
Occluded graft	11
Patent graft	5
Progression of disease (≥75% narrowing) in other vessels	8
LAD graft	8
LCx graft	6
Patients reoperated on	8
RCA graft	4
LAD graft	1
LAD + LCx grafts	1
RCA + LAD grafts	1
RCA + LAD + LCx grafts	1

* Data from eight patients reoperated on are not included.
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

The subjective assessment of patients' pain relief at the time of latest follow-up is presented in Figure 2. Sixty percent of the patients are entirely free of angina, and 43 percent of them have returned to full-time work or full physical activity, or both. Twenty-six percent of patients have decreased symptoms. Fourteen percent were considered to have derived no benefit from the initial procedure because of a recurrence of or increase in angina, a late myocardial infarction or death due to a cardiovascular event.

Discussion

The effects of coronary bypass surgery on the natural history of ischemic heart disease may be assessed by various criteria: mortality versus increase in longevity, operative and postoperative morbidity, symptomatic relief and postoperative functional capacity. To assess adequately the value of surgical intervention, an understanding of the natural history of ischemic heart disease is necessary. Although numerous studies address this topic, the most accurate and reliable means of predicting survival has been obtained since the development of coronary arteriography and left ventriculography. To our knowledge, only two studies[7,9] fulfill the criteria of (1) adequate numbers of patients to allow statistical significance, (2) a minimum of 5 years' follow-up after angiography, and (3) homogeneity of groups studied, for example, single, double and triple vessel disease. These studies confirm the relatively low mortality rate of single vessel coronary disease, and specifically of occlusive disease confined to the right coronary artery. Burggraf and Parker[9] state, "... the excellent prognosis in the group with single vessel disease, particularly those with isolated right coronary artery narrowing, provides a strong argument against

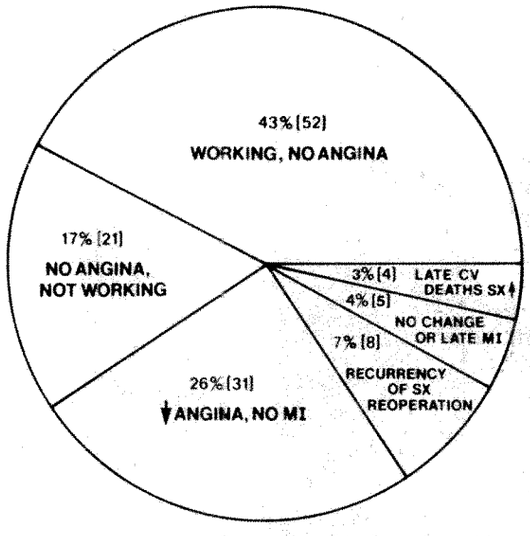


FIGURE 2. Symptomatic results in 121 patients at time of latest follow-up (mean 3.7 years, range 1.0 to 7.5). The data are based on exclusion of two patients who died at operation and one patient who died of carcinoma of the lung. CV = cardiovascular; MI = myocardial infarction; Sx = symptoms; ↓ = decreased; ↑ = increased.

the application of surgical treatment to this group." However, the studies mentioned did not classify patients according to functional capacity and clinical status. In this regard several aspects of our study group deserve emphasis. In nearly all cases, surgical intervention was undertaken for the relief of symptoms, which were severely incapacitating in 75 percent of our patients (New York Heart Association class III or IV preoperatively), although the majority had been treated with long-acting nitrates or propranolol, or both. Unstable angina was the presenting feature in 9 percent, and 5 percent exhibited life-threatening ventricular tachyarrhythmias.

Survival after surgical versus medical treatment of isolated right coronary artery disease: Being fully cognizant that only prospective double blind studies can ultimately answer the question of the effects of coronary artery bypass surgery on the improvement of longevity, it is nevertheless informative to compare the yearly mortality rate of our patients with the two groups of patients having angiographically documented obstructive disease confined to the right coronary artery[7,9] (Fig. 3). The 5 year mortality rate in our patients was 4.0 percent, whereas that of the two medically managed groups ranges from 2 percent in the study of Burggraf and Parker[9] to 10 percent in that of Bruschke et al.[7] It is widely accepted that coronary bypass surgery now plays a major role in the management of ischemic heart disease, with amelioration of symptoms often being the primary goal of the procedure. Various authors[3,19] have reported that 60 to 70 percent of patients were completely asymptomatic 12 to 24 months postoperatively, with approximately 90 percent experiencing symptomatic benefit. This may be contrasted with reports of patients managed medically,[4,20,21] of whom only 55 percent had symptomatic improvement and 10 to 25% were free of angina 24 months after the diagnosis of angina pectoris. More recently Lawrie et al.[3] reported on the long-term follow-up (mean 70.7 months) of 273 patients undergoing coronary bypass surgery. They found that 93.4 percent of their patients had a decrease in angina and that 51.3 percent were entirely free of angina. Our data compare favorably with their data and that of others.[3,4,10] Postoperatively, the condition of 104 patients (86 percent) improved by one or more functional class, 73 patients (60 percent) are entirely free of angina and 52 patients (43 percent) have returned to full-time work.

Perioperative myocardial infarction and progression of coronary disease: The incidence of perioperative myocardial infarction in our series was 5 percent. Dunkman et al.[19] noted an average 7 percent incidence rate of perioperative myocardial infarction in studies not specifically designed to identify this event, and a 21 percent incidence rate in six studies specifically seeking the occurrence of perioperative myocardial infarction. One third of the patients in our series with a perioperative myocardial infarction died. In view of a coronary care unit mortality rate of 10 to 25 percent for spontaneous myocardial infarction and the fact that our patients had single vessel disease whereas a large percentage of coronary care unit patients have multivessel disease, perioperative myocardial infarction appears to have more adverse effects on survival than has spontaneous infarction.

The progression of disease seen in ungrafted vessels is also of interest. A recent[3] long-term follow-up study of patients undergoing coronary bypass surgery revealed completely new lesions (greater than 70 percent stenosis) at previously angiographically normal sites in 10.7 percent of all vessels and in 10 percent of ungrafted vessels. In contrast, new lesions developed in grafted vessels at a rate of only 3.3 percent. Although no conclusions may be drawn from our sample, significant new

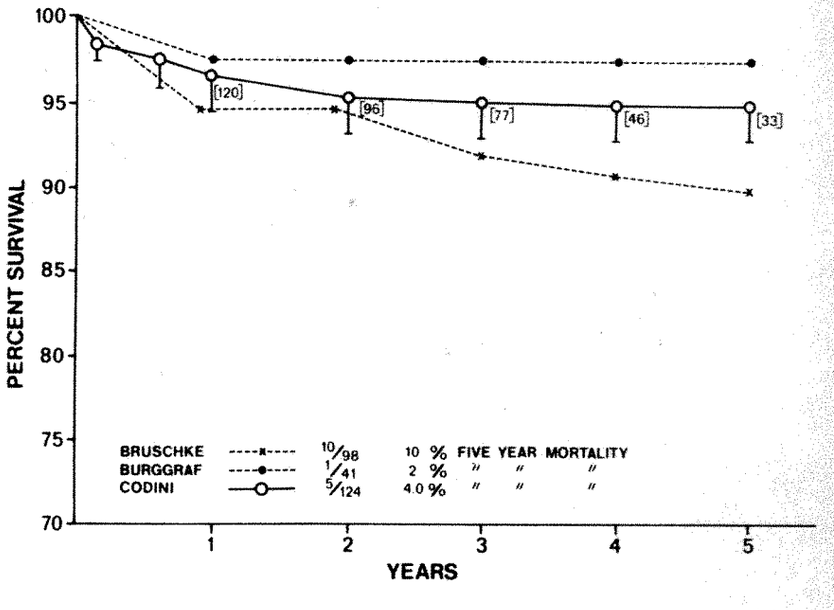


FIGURE 3. Survival rates in two medically treated groups[7,9] of patients with occlusive disease confined to the right coronary artery compared with the survival rate obtained in our study. Survivors of the medically treated groups were followed up for a minimum of 5 years. The numerals below the **continuous line** represent the number of patients followed up in our study. The **vertical bars** indicate the standard error of survival probability.

disease developed in angiographically defined previously normal vessels in 27 percent of our patients who were restudied.

Implications: It appears that, although saphenous vein bypass surgery for isolated obstructive disease of the right coronary artery does not enhance the favorable prognosis of patients with this lesion, it provides excellent long-term symptomatic improvement at acceptable levels of risk. In patients operated on, the finding of normal or nonobstructive disease (less than 50 percent luminal narrowing) of the remaining coronary arteries does not alter the need for very close follow-up, possibly including serial coronary arteriography. Coronary bypass surgery for isolated obstructive disease of the right coronary artery is justified in highly symptomatic patients or in patients with malignant tachyarrhythmias, or both.

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Revascularization of the Right Coronary Artery

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This study was undertaken to evalulate revascularization of the right coronary artery with regard to factors that enter into the decision to graft less significant lesions, such as graft flow, graft patency and progression of proximal disease. The results of grafting the right coronary artery were studied in 23 patients with lesions reducing luminal diameter by less than 50 percent (Group 1), 35 patients with luminal narrowing of 50 to 70 percent (Group 2) and 112 patients with greater than 70 percent luminal narrowing (Group 3). At operation there was no significant difference in saphenous vein graft flows among the three groups. Postoperatively the mean follow-up period was 20, 27 and 26 months, respectively. Graft patency was not significantly different among the three groups. Progression of the proximal lesion was studied and compared with that in 71 ungrafted right coronary arteries, 60 with less than 50 percent stenosis and 11 with more than 50 percent stenosis. Among vessels with less than 50 percent narrowing, the proximal lesion showed progression in 26 percent of the ungrafted vessels and in 83 percent of the grafted vessels ($P < 0.005$); progression to total occlusion occurred in 3 percent of the former and in 28 percent of the latter ($P < 0.005$). Progression to total occlusion was more frequently associated with a patent than with an occluded graft ($P < 0.05$). The occurrence of significant progression in ungrafted vessels and the lack of effect on graft patency of the severity of the proximal disease suggest that revascularization of less significant lesions may be of value. However, the resultant increase in progression of proximal disease makes the patient dependent on the long-term patency of the vein graft.

Bypass grafting is generally not performed when an obstructive lesion of less than 70 percent in luminal diameter involves a single coronary artery. However, when other vessels are being grafted, the question arises whether grafting should be performed in a right coronary artery with an obstructive lesion of less than 70 percent. One argument in favor of such grafting is that the lesion may progress and require reoperation. Siedes et al.[1] found that progression of disease in ungrafted vessels accounted for recurrence of angina in 9 of 11 patients with postoperative symptomatic deterioration. On the other hand, it has been suggested that because of competitive flow through an insignificantly obstructed native coronary artery, graft flow may be low and graft patency reduced.

An argument against grafting arteries with less significant lesions was the demonstration by Aldridge and Trimble[2] and subsequently by others[3–24] that grafting of a coronary artery may result in increased progression of the proximal lesion. This results in dependence of the distal coronary artery on the vein graft and its long-term patency. This study was undertaken to evaluate the factors, that enter into the consideration to graft right coronary arteries with various degrees of obstruction.

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TABLE I

Patients With Stenosis of the Right Coronary Artery Undergoing Catheterization at Each Time Interval

Stenosis Group	Patients: Total no.	Total With Recatheterization (no.): 0–6 Mo	1 Yr	3 Yr	5 Yr	Mean Follow-Up Period (mo)
1 (<50%)	23	23	16	7	2	20
2 (50–70%)	35	34	27	12	8	27
3 (>70%)	112	109	63	41	21	26
Total	170	166	106	60	31	24

Methods

Patients: One-hundred seventy patients, 143 men and 27 women, who underwent revascularization of the right coronary artery at St. Louis University from 1970 to 1976 were included in this study. They were separated into 23 consecutive patients with 0 to 50 percent obstruction of luminal diameter (Group 1) and 35 consecutive patients with 50 to 70 percent obstruction (Group 2). During this period a total of 544 patients with stenotic lesions of the right coronary artery of greater than 70 percent underwent revascularization. Of these, 112 (Group 3) were randomly selected so that the number included for each year of the study was proportional to that of Groups 1 and 2. These three groups were compared with 71 patients who were not treated surgically, although coronary arteriography during the same period revealed lesions of the right coronary artery. Patients with a small right coronary artery unsuitable for grafting were not included in this group. There were 60 patients with less than 50 percent narrowing and 5 patients with 50 to 70 percent narrowing. Six patients had right coronary arterial lesions greater than 70 percent, but grafting was not performed because of the presence of diffuse disease.

At operation, the size of the right coronary arterial lumen was measured with calibrated probes. At the completion of cardiopulmonary bypass, flow in the vein grafts to the right coronary artery was measured with the use of electromagnetic flow probes.

Follow-up coronary arteriography: Graft patency has been systematically studied with repeat cardiac catheterization at St. Louis University since 1970. Repeat catheterization using the Judkins technique was performed 0 to 6 months and 1, 3, and 5 years after operation. Both the native coronary arteries and the vein grafts were selectively injected and viewed in multiple projections. The same observers graded the lesions and reviewed the previous films at each catheterization for comparison. Lesions were graded according to the decrease in luminal diameter seen in two views, and were classified into three groups: those with less than 50 percent narrowing, those with 50 to 70 percent obstruction and those with greater than 70 percent obstruction. All patients were routinely called for recatheterization, and the number of patients from each group who were studied at each time interval and the mean follow-up period are shown in Table I.

TABLE II

Luminal Size Measured at Operations in Native Right Coronary Artery Undergoing Grafting

Stenosis Group	Cases (no.)	Luminal Size: 1 mm (%)	1.5 mm (%)	2 mm (%)	2.5 mm (%)
1 (<50%)	23	0	0	30	70
2 (50–70%)	35	0	8	34	58
3 (>70%)	112	4	8	39	49

TABLE III

Flow in Vein Grafts to the Right Coronary Artery

Stenosis Group	Cases (no.)	Mean Flow (ml/min)	no. With Flow <40 ml/min: no.	%
1 (<50%)	23	70.5	7	32
2 (50–70%)	35	72.6	9	26
3 (>70%)	112	72.2	23	21

Results

Findings at surgery: The size of the coronary lumen found in the three groups is shown in Table II. A greater proportion of patients in Groups 2 and 3 than in Group 1 had a right coronary arterial lumen of 2.5 mm or greater although this difference was not statistically significant.

The flows measured in the grafts to the right coronary artery in the three groups are shown in Table III. There was no significant difference among groups. Although there were more grafts with flows of less than 40 ml/min to the vessels with less severe stenosis, this difference was not statistically significant.

Graft patency: The overall graft patency rate (Table IV) on the basis of the last catheterization performed was 91 percent for Group 1, 74 percent for Group 2 and 80 percent for Group 3. The mean follow-up period was 20, 27 and 26 months, respectively. These differences were not statistically significant. The cumulative graft patency rate for the three groups calculated by the life table method is shown in Figure 1. The 3 and 5 year patency rates reflect the small number of patients undergoing catheterization at this time period.

The relation between graft flow measured at operation and graft patency is shown in Table V. In each group, the patency rate was lower when the flow was less than 40 ml/min, but the difference was not statistically significant. Nine of the 112 patients in Group 3 had an endarterectomy, all in vessels with 100 percent occlu-

TABLE IV

Patency of Grafts to the Right Coronary Artery

Time After Operation	Patients With Catheterization	Percent With Patent Grafts: Group 1 (<50% stenosis)	Group 2 (50–70% stenosis)	Group 3 (>70% stenosis)
6 mo	166	91 ± 13	88 ± 11	92 ± 5
1 yr	106	91 ± 0	75 ± 12	86 ± 3
3 yr	60	91 ± 0	59 ± 19	81 ± 6
5 yr	31	91 ± 0	59 ± 0	51 ± 22
Overall patency*	170	91	74	80

* At time of last catheterization. There was no statistical difference among the patency rates in the three groups.

TABLE V

Relation of Measured Flow in Grafts to Patency of the Right Coronary Artery and Graft

Stenosis Group	Cases (no.)	Flow <40 ml/min		Flow >40 ml/min		Overall Patency Rate (%)
		no.	% Patent	no.	% Patent	
1 (<50%)	23	7	85	15	93	91
2 (50–70%)	35	9	66	26	76	74
3 (>70%)	112	23	78	87	85	80

TABLE VI

Patency of Vein Grafts to Other Vessels Compared With Patency of Vein Grafts to the Right Coronary Artery

Stenosis Group	Overall RCA Graft Patency		Patency of Other Vein Grafts		Patency of IMA Grafts	
	no.	%	no.	%	no.	%
1 (<50%)	23	91	18	83	10	70
2 (50–70%)	35	74	39	77	12	83
3 (>70%)	112	80	127	76	27	96
Totals	170	81	184	77	49	88

IMA = internal mammary artery; RCA = right coronary artery.

sion. Six of the nine grafts were patent at recatheterization, a mean of 17 months postoperatively.

The patency of grafts performed to other vessels is shown in Table VI. There was no significant difference in patency between vein grafts to the right coronary artery and vein grafts or internal mammary artery grafts to other vessels.

Progression of proximal disease: This was compared among three groups with grafting and the groups without grafting (Table VII). Progression was defined as an increase in the obstruction to a higher group (for example, from less than 50 percent to 50 to 70 percent obstruction) or progression to total occlusion. Lesser degrees of progression of disease were not included. In Group 3, there were 51 patients who had complete occlusion of the native right coronary artery preoperatively and were therefore excluded from the study of progression. The rate of progression was significantly higher for the grafted than the nongrafted vessels in comparing vessels with lesions of less than 50 percent ($P < 0.005$). The small number of patients in Groups 2 and 3 without grafting makes comparisons difficult. Progression to total occlusion may be a more objective assessment of disease progression. As shown in Table VII, the proximal lesion progressed to total occlusion more frequently in the groups with than in those without grafting. This difference was statistically significant ($P < 0.005$) for vessels with lesions less than 50 percent and for vessels with lesions greater than 70 percent.

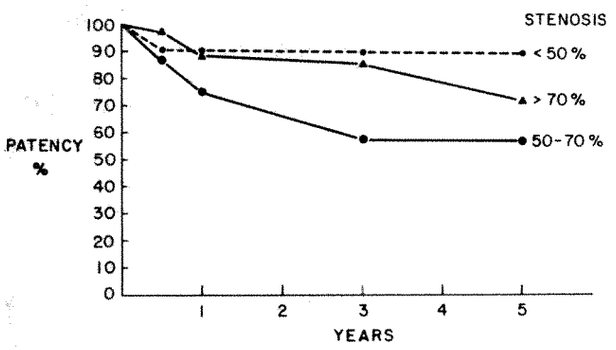


FIGURE 1. Cumulative patency rate of vein grafts to the right coronary artery calculated with the life table method is shown. There was no statistical difference in graft patency among the three groups.

The progression of the proximal disease was also related to graft patency (Fig. 2). In all three groups there was a significantly greater incidence of graft patency in those vessels with lesions that progressed to total occlusion than in those that did not ($P < 0.05$).

Discussion

Factors influencing vein graft flow: The concept of competitive flow between a vein graft and the native coronary artery has been studied experimentally. Furuse et al.[25] found that a relatively small vein graft anastomosed to the nonobstructed circumflex coronary artery of the dog carried 73.7 percent of the total flow and a large graft carried 95.1 percent of the flow. However, with a 50 percent obstruction to the native circumflex vessel, vein graft flow was always greater than 90 percent of the total flow. Kakos et al.[26] reported similar results, with the vein graft assuming 50 percent to 100 percent of the flow depending on the degree of proximal stenosis. These studies explain the similarity

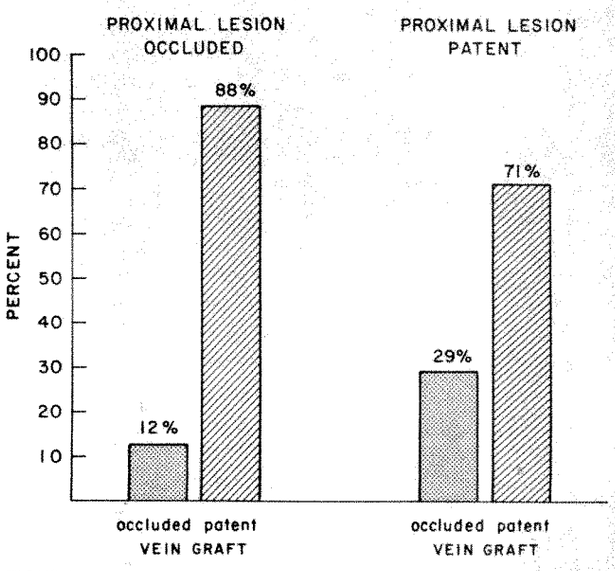


FIGURE 2. Effect of vein graft patency on the progression of the proximal right coronary arterial lesion to total occlsuion. There were significantly more patent grafts to vessels in which the proximal lesion progressed to total occlusion than to vessels with a patent proximal lesion ($P < 0.05$).

TABLE VII

Progression of Proximal Lesion and Progression to Total Occlusion in Grafted and Ungrafted Right Coronary Arteries (RCA)

Stenosis Group	Progression of Proximal Disease*				Progression to Total Occlusion*			
	Ungrafted RCA		Grafted RCA		Ungrafted RCA		Grafted RCA	
	no.†	%‡	no.	%‡	no.†	%‡	no.†	%‡
1 (<50%)	60	26	18	83§	60	3	18	28§
2 (50–70%)	5	60	29	62	5	20	29	14
3 (70–99%)	6	67	43	86	6	16	43	74§

* The column headed "Progression of Proximal Disease" includes lesions that progressed to total occlusion, which are also given separately under the heading "Progression To Total Occlusion."
† no. = total number in group.
‡ % = percent of group with progression of disease or new total occlusion.
§ $P = <0.005$.

of flows between grafts to severely obstructed and mildly obstructed right coronary arteries in our cases. The resistance posed by the relatively narrow native coronary artery is far greater than that in the relatively large vein graft and the latter therefore assumes the majority of the flow even in a mildly obstructed vessel.

The measurements of luminal size of the native coronary arteries indicate that large vessels were more common in the group with less than 50 percent obstruction, and 70 percent of the vessels in this group had a luminal diameter of 2.5 mm or more compared with 58 percent in the group with 50 to 70 percent obstruction and 49 percent in the group with greater than 70 percent obstruction. These data indicate that there was some preselection of the patients with lesions less than 70 percent based on the size of the native coronary artery. The vessel size would probably also influence graft flow because of the size of the runoff and graft patency because of the greater technical ease of the anastomosis.

Vein graft patency: The patency of the vein grafts to the three groups of stenotic right coronary arteries (obstruction of less than 50 percent, 50 to 70 percent and more than 70 percent) was not significantly different. It has previously been shown that there is a correlation between graft occlusion and basal graft flow of less than 40 ml/min.[17,27] The number of grafts with flow rates in this range in the three groups was found to be similar. Although in each group the patency rate was less with flows of less than 40 ml/min this difference was not statistically significant. The cumulative graft patency rate determined with the life table method showed no difference among the three groups. The low patency rates at 3 and 5 years may reflect the small number of patients undergoing catheterization at these intervals. These patency rates are similar to those reported by others for overall graft patency and were similar to the patency rates for grafts to other vessels in this series (Table VI).

Progression of native coronary artery disease: Progression of disease proximal to a vein graft was first reported by Aldridge and Trimble[2] and has been confirmed in several studies.[3–24] Our study also confirmed previous reports[7] that progression of disease is more common with greater initial stenosis. In the ungrafted vessels of our series the rate of progression of disease was higher than that reported by others[3,5,13] as was the rate of progression in bypassed vessels with mild lesions.[11] Lawrie et al.[11] found that only 4 percent of mild lesions became "clinically significant." However, comparative angiograms obtained before and after operation were available in only 75 of the 434 patients in their study. Progression of disease to total occlusion may be a more objective test of progression. In our study progression to total occlusion was significantly more common in the grafted than in the ungrafted vessels (P <0.005) and was, as expected, more common in arteries with greater than 70 percent narrowing (Table VII).

Graft patency and proximal disease progression: There have been varying reports of this relation. Griffith et al.[3] and others[5,18] found that proximal occlusion was more common with early graft occlusion, a finding that may be related to technical factors resulting in thrombosis at the anastomosis. Other reports have shown a greater incidence of proximal progression associated with a patent graft. Bourassa et al.[5] found proximal progression in 58 percent of patients with a patent graft and in 40 percent with an occluded graft. McLaughlin et al.[9] found proximal progression in 43 percent of arteries with a patent graft and in 13 percent of those with an occluded graft. Similar findings were reported by Pasternak[7] and Lawrie[10] and their co-workers. We found that progression to total occlusion was associated with a patent graft in 88 percent of cases and with an occluded graft in 12 percent. There was a statistically significant correlation between graft patency and progression of proximal disease (P <0.05). Progression of proximal disease has been ascribed to a reduction in flow in the proximal segment, which has been demonstrated experimentally.[25,26,28] It would therefore be expected that this would be more common with a patent than with an occluded graft.

Clinical implications: The clinical decision to graft a right coronary artery with less than 70 percent obstruction is influenced by the fear that residual disease in an ungrafted vessel may progress, which has been reported to be an important cause of recurrence of symptoms.[1] There was a relatively large incidence of progression of disease in ungrafted vessels with 50 to 70 percent narrowing, 20 percent of these vessels progressing to total occlusion in this small group of patients.

Even in the group with ungrafted vessels with lesions of less than 50 percent, 26 percent of vessels progressed to greater than 50 percent obstruction and 3 percent became totally occluded. Because our study has shown that graft flow and patency are unaffected by the severity of proximal disease, we currently perform coronary bypass grafting in all right coronary arteries with a lesion of 50 percent or greater. For lesions of less than 50 percent we would be influenced by the dominance of the vessel, the ability to revascularize other vessels and the age of the patient. In this situation the vessel is being bypassed prophylactically, and occlusion, due to technical problems or complications, could result in myocardial infarction. The high rate of progression of proximal disease and occlusion, once the vessel is bypassed, makes the vessel totally dependent on vein graft patency. However, studies of long-term graft patency indicate that if the graft remains patent for the first few months, it is likely to remain patent for the ensuing 5 to 7 years.[1,10,30] The ultimate resolution of this question depends on even longer-term follow-up studies of vein graft patency.

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Poststress Redistribution of Thallium-201 in Patients With Coronary Artery Disease, With and Without Prior Myocardial Infarction

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To elucidate patterns of thallium-201 redistribution with and without myocardial infarction, to determine the value of thallium-201 redistribution scintigrams in identifying additional ischemic myocardium in the presence of prior myocardial infarction and to delineate the relation of collateral vessels to redistribution, thallium-201 myocardial perfusion scintigraphy was performed immediately after exercise and 4 to 6 hours after exercise in 46 patients with coronary artery disease and 12 normal control subjects. Scintigrams were interpreted in the conventional visual manner as well as with use of computer-processed myocardial perfusion ratios. Normal control subjects demonstrated uniform thallium-201 distribution with regional perfusion ratios approximating unity in both the early and delayed scintigrams.

Of 27 patients with prior myocardial infarction, 5 (19 percent) had complete redistribution on delayed imaging, 17 (62 percent) had partial redistribution and 5 (19 percent) had no redistribution. Of 25 regions corresponding to electrocardiographic evidence of infarction, 8 (32 percent) had total, 8 (32 percent) had partial and 9 (36 percent) had no redistribution. Collateral vessels were absent or of poor quality in seven of eight infarct areas with no redistribution; three of four infarct regions with normal early thallium uptake were supplied by collateral vessels of good quality. Of 12 regions supplied with good collateral vessels, 9 had complete redistribution, 2 partial and 1 no redistribution. In contrast, only 2 of 21 hypoperfused zones without redistribution (10 percent) were supplied by good collateral vessels. Of 19 patients without prior myocardial infarction, 10 (53 percent) had complete redistribution, 6 (31 percent) had partial redistribution and 3 (16 percent) had no redistribution. Of the 34 abnormal areas in the immediate postexercise image, 22 (65 percent) showed total redistribution, 3 (9 percent) showed partial redistribution and 9 (26 percent) showed no redistribution.

Thus, considerable overlap in redistribution scintigrams occurs in patients with coronary artery disesase with and without prior infarction; a high incidence rate of transient stress-induced hypoperfusion occurs in both infarcted and noninfarcted myocardium. Further, good quality collateral vessels afford redistribution, even to some areas of prior infarction. These data indicate that because delayed postexercise redistribution imaging may not discriminate between myocardial scar and ischemia resting scintigrams may be needed in a substantial number of patients.

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Thallium-201 myocardial perfusion imaging has become an important diagnostic tool in the evaluation of patients with coronary artery disease. The greatest sensitivity of myocardial perfusion imaging in detecting significant coronary artery disease is achieved when thallium-201 is injected during maximal stress.[1–5] To differentiate a stress scintigram

abnormality due to transient ischemia from one due to previous myocardial infarction, a second injection of thallium-201 at rest has ordinarily been performed 4 or 5 days before or after the stress scintigram. Recently it has been indicated in the experimental animal[6,7] and clinically[6,8,9] that delayed scintigrams obtained 4 to 6 hours after the initial poststress imaging permit distinction between transient ischemia and infarcted myocardium, because only areas of infarction demonstrate persistent reduction of thallium-201 activity.

Additional detailed information is needed concerning the clinical importance of, as well as functional and anatomic correlations with, the variable patterns of postexercise thallium-201 redistribution. Accordingly, we performed stress myocardial perfusion imaging and obtained early as well as delayed scintigrams in patients with documented coronary artery disease with and without prior myocardial infarction in order to elucidate the postexercise redistribution patterns of thallium-201 in these patients. Additionally, we assessed the presence and quality of coronary collateral vessels to afford insight concerning the possible role of these vessels in determining redistribution.

Methods

Patient groups: The patient population consisted of 58 patients who underwent sequential thallium-201 imaging. *Group I* contained 12 patients with a mean age of 50 years who had chest pain atypical of angina, no coronary artery disease (no stenosis greater than 50 percent of luminal diameter) on selective coronary arteriography, normal left ventricular function and no systemic hypertension or left ventricular hypertrophy.

Group II consisted of 27 patients with a mean age of 52 years who had a previous myocardial infarction confirmed by a typical history and diagnostic enzymatic and electrocardiographic alterations. With the exception of one patient who had a documented history of myocardial infarction and left bundle branch block, all patients in Group II exhibited pathologic Q waves consistent with prior myocardial infarction. In addition, selective coronary arteriography demonstrated stenoses of 50 percent or more in one or more of the three principal coronary arteries in all 22 patients with a prior infarction undergoing cardiac catheterization.

Group III consisted of 19 patients with a mean age of 59 years who had typical angina pectoris but no previous history or electrocardiographic documentation of myocardial infarction. All 12 of these 19 patients who underwent selective coronary arteriography demonstrated significant stenosis (50 percent or greater) in one or more of the major coronary arteries. Of the remaining seven patients, all had typical angina, five had ischemic S-T segment depression (1.0 mm or more flat or downsloping 0.08 second beyond the J point) on treadmill stress testing and two had a nondiagnostic test because of failure to reach 85 percent of the maximal predicted heart rate. Because this investigation was designed to assess the temporal characteristics of myocardial redistribution of thallium-201, the patients in Groups II and III were selected so that all had abnormal early poststress myocardial perfusion imaging.

To determine whether the presence of coronary collateral vessels influenced the redistribution scintigram, arteriographic coronary collateral vessels were graded using a modification of the system proposed by Carroll et al.[10]: 0 = no collateral channels present; 1 = small, threadlike collateral channels without distal opacification of the recipient occluded coronary artery; 2 = moderate-sized collateral channels with faint but definite opacification of the distal recipient vessel; 3 = large, bright collateral channels with excellent opacification of the distal recipient vessel. For purposes of analysis, grades 0 and 1 were grouped together as were grades 2 and 3.

Thallium-201 myocardial perfusion imaging: All patients underwent multistage treadmill exercise according to the protocol of Bruce.[11] Thallium-201 (1.5 to 2 mCi) as thallous chloride in saline solution was injected through a previously placed intravenous cannula in one arm and flushed with 5 cc of saline solution at peak exercise, which was determined by increasing angina, 2 mm or more flat or downsloping S-T segment depression of at least 0.08 second's duration in at least 1 of the 12 monitor leads, severe fatigue, dyspnea or claudication. The exercise was continued for an additional 0.5 to 1 minute after the injection to allow for clearing of thallium-201 from the blood. Imaging was then initiated within 5 minutes of the injection in every patient.

A commercially available single crystal gamma camera equipped with an all-purpose, parallel hole collimator was utilized for imaging. Counting was done with the pulse-height analyzer centered at 75 kev employing a 20 percent window. Images were obtained in anterior and 40° left anterior oblique projections. A total of 300,000 counts requiring 3 to 5 minutes for collection were obtained in each position. Images in the identical projections were repeated 4 to 6 hours after the treadmill exercise. The data were collected and stored in a dedicated computer with capabilities for color display, contrast enhancement, background subtraction and smoothing. The scintigrams were stored in floppy discs for later display and were subsequently interpreted on a 128/128 matrix oscilloscope by two of us independently and without knowledge of either the arteriographic or the electrocardiographic findings.

Scintigraphic analysis: Each scintigram was divided into the following five segments for the purpose of reproducible analysis: anterior, inferior, septal, apical and posterolateral (Fig. 1). A region of interest with constant area was delineated

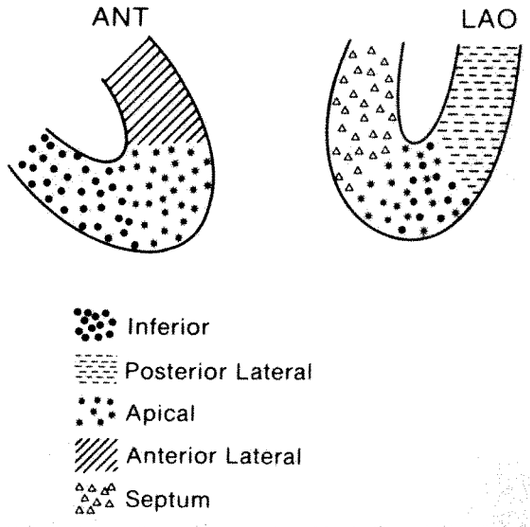


FIGURE 1. Myocardial regions analyzed in thallium-201 scintigrams. ANT = anterior; LAO = left anterior oblique.

TABLE I

Perfusion Ratios in Three Groups

Myocardial Segments	Group I: (normal subjects)	Group II: (prior MI)	Group III: (CAD)
Ant ST	1.030 ± 0.020	0.746* ± 0.012	0.926 ± 0.089
Ant RT	1.024 ± 0.015	0.849† ± 0.048	0.863* ± 0.030
Inf ST	0.974 ± 0.018	0.684* ± 0.029	0.783* ± 0.038
Inf RT	0.977 ± 0.014	0.813* ± 0.032	0.917 ± 0.054
IVS ST	0.981 ± 0.021	0.664* ± 0.038	0.776* ± 0.033
IVS RT	1.003 ± 0.028	0.855† ± 0.054	0.925 ± 0.028
PL ST	1.024 ± 0.022	0.755* ± 0.045	0.791* ± 0.020
PL RT	0.994 ± 0.025	0.806 ± 0.084	0.895† ± 0.025
Apex ST	0.916 ± 0.019	0.713* ± 0.037	0.747* ± 0.033
Apex RT	0.899 ± 0.034	0.775† ± 0.033	0.827 ± 0.026

* Probability (P) ≤0.001 (versus Group I).
† P ≤0.05 (versus Group I).
Ant = anterior wall; CAD = coronary artery disease; Inf = inferior; IVS = interventricular septum; MI = myocardial infarction; PL = posterolateral; RT = delayed (resting) scintigram; ST = immediate post-stress scintigram.

in each segment, and the absolute number of counts was obtained from the computer memory.

To afford semiquantitative analysis and thereby enhance objectivity in the interregional comparisons, a count-ratio method was utilized. A ratio was determined from the counts in an area of interest in each specified region to a normal area of myocardium defined as the zone in each separate projection with the highest count density. In the normal scintigrams, the area of interest was obtained from the center of each defined region. In the abnormal scintigrams, for the purpose of consistent location of the region of interest in each individual segment, a color display was used to facilitate the location of the abnormal areas. With this color display, a difference of counts of the order of 12.5 percent can be appreciated. Thus, small differences in perfusion could be easily uncovered visually. The regions of interest in the abnormal segments were selected as representative of a portion of the most abnormal perfusion. Assuming that the areas of maximal perfusion in each projection represented normal perfusion, the derived ratio between the two segments multiplied by 100 corresponds to the percent of normal perfusion in the abnormally perfused segment. For example, a ratio of 1 would be expected to represent a normal value with homogeneous perfusion.

Because most previous investigators have reported myocardial scintigrams based on a visual interpretation only, we also used this visual technique in the final report of the scintigrams to permit uniform comparison with previous studies. Visual interpretation of perfusion defects and degree of reperfusion was accomplished in computer-processed black and white scintigrams after 20 percent background subtraction according to a grading scale: 0 = no redistribution; + = partial redistribution; ++ = complete redistribution. Complete agreement on visual interpretation was obtained in 88 percent of the cases. In the remaining 12 percent, a consensus was generally reached by review of the scintigram and discussion between the two interpreters. If no agreement was reached (4 percent), an increase in the count-ratio (involved area/normal area) of more than 20 percent was utilized as objective evidence of redistribution.

Statistical method: Student's t test for paired and nonpaired data was utilized to assess the significance of differences in ratios for each of the patient groups in the early and delayed scintigrams. A test of equality of variances was used to assess the differences in ratios between the groups. The results are expressed as the mean ± standard error of the mean.

Results

Group I: Patients Without Coronary Artery Disease

Table I summarizes the perfusion ratios obtained from the early and delayed scintigrams in the 12 normal patients. Two of these patients received propranolol up to 12 hours before the first scintigram was obtained. Despite normal immediate postexercise images in each patient, six also had delayed scintigrams to determine reproducibility of the myocardial perfusion ratios in this control group. The mean values for each ratio were near unity in both the early and delayed images for all anatomic regions indicating normal homogeneous perfusion. Perfusion at the apex exhibited the greatest variability, which may be explained by the normal thinning of this region. Visual interpretation of the scintigrams revealed a homogeneous perfusion throughout the myocardium, except for small areas (less than 15 percent of the total) of relative hypoperfusion sometimes observed in the apex.

Group II: Patients With Prior Myocardial Infarction

Seventeen of the 27 patients with a prior infarction underwent cardiac catheterization because of postinfarction angina. The remaining five patients who underwent coronary arteriography did not have a history of angina, but underwent catheterization for prognostic reasons. Table II summarizes the results of the resting electrocardiograms, treadmill stress tests, coronary arteriography and thallium-201 perfusion imaging for these 27 patients. At the time of imaging, all patients demonstrated electrocardiograms diagnostic of prior infarction with the exception of one patient with left bundle branch block. Seven of the 27 patients in this group were receiving propranolol in an average daily dose of 80 mg, 3 were taking a digitalis preparation and 2 patients were receiving both propranolol and digitalis; the remaining 15 patients were taking no cardiac medication. A total of 33 anatomic sites of infarction were detected with the resting electrocardiogram in the 26 patients with infarction. With maximal treadmill stress testing, 11 of the 26 patients (42 percent) had ischemic S-T segment depression, 11 (42 percent) experienced angina pectoris and 14 (54 percent) had either angina or S-T segment abnormalities. The majority (17) of the 22 patients in Group II who underwent coronary arteriography had multivessel disease: 10 (45 percent) and 7 (32 percent) had three and two vessel disease, respectively; 5 (23 percent) had stenosis of one major coronary artery.

Mean perfusion ratios for each of the five regions evaluated (Table I): Patients with prior myocardial infarction, when compared with normal subjects, demonstrated significant (P <0.05) reduction in perfusion on both immediate and delayed imaging in all regions with the exception of the posterolateral area on delayed imaging (P >0.05). There was no statistically significant difference (P >0.05) between the perfusion

TABLE II

Findings in 27 Patients in Group II (prior myocardial infarction)

Case		Treadmill Stress Test					Cineangiography				MPI	
no.	ECG	Time	Angina	HR	ST	DP	RCA	LAD	LCx	LV	EMPI	DMPI
1	Inf;AL	4′40″	Pos	123	Pos	17.2	90	90	80	Diff hypok	Inf,	+
											IVS,	++
											Ap	+
2	Inf;IVS	6′	Pos	155	Pos	24.8	100	100	80	Inf Ap hypok	Inf,	++
											IVS,	++
											Ap	0
3	Inf	5′	Pos	135	Pos	24.3	100	—	—	NL	Inf	++
4	Inf	11′	Pos	133	ND	23.9	80	40	90	Inf bas hypok	Inf,	++
											IVS	++
5	Inf	2′	Neg	115	Pos	16.1	100	95	99	Inf bas hypok	PL,	++
											Ap	++
6	Ant;Inf	11′	Neg	145	Neg	23.2	100	100	90	Ap dysk, inf bas hypok	Ant,	0
											Ap	++
7	Inf;IVS	11′	Neg	162	Neg	20.4	100	90	70	Inf Ap hypok	Inf,	++
											IVS,	+
											Ap	++
8	Inf	8′30″	Neg	172	Pos	30.9	100	—	100	Diff hypok, inf bas akin	Inf	0
9	IVS	5′50″	Pos	120	Pos	18.0	70	100	90	Inf, Ap hypok	Ant,	++
											IVS,	0
											Ap	0
10	Inf	9′30″	Neg	170	Neg	20.4	100	—	—	Inf bas hypok	Inf,	++
											Ap	++
11	Inf	5′15″	Neg	158	Neg	22.1	95	—	80	Inf akin	Inf	0
12	Inf	8′40″	Neg	145	Neg	17.4	95	—	—	Inf bas hypok	Inf	0
13	AL	11′	Neg	153	Neg	26	—	90	90	Ant Ap dysk	Ant,	0
											IVS,	0
											Ap	+
14	Inf	7′20″	Neg	123	Pos	22.1	100	50	95	Inf bas hypok	Inf,	+
											IVS	++
15	IVS	10′	Neg	160	Neg	25.6	90	100	—	Ant hypok	IVS,	++
											Ap	0
16	IVS	8′20″	Neg	140	ND	26.6	99	80	30	NL	Inf,	+
											PL,	+
											Ap	0
17	Inf	4′	Pos	88	Pos	14	100	40	—	Inf bas akin	Inf,	0
											PL,	0
											Ap	++
18	Ant(SE)	5′30″	Pos	120	Pos	16.8	50	90	50	Ant Ap hypok	Ant,	++
											IVS,	0
											Ap	0
19	Inf	4′15″	Pos	135	Pos	21.6	100	90	100	Ap hypok	Ant,	++
											IVS,	++
											Ap	++
20	Inf	8′30″	Neg	170	Neg	32.2	—	80*	—	NL	Inf,	+
											PL	0
21	LBBB	2′30″	Neg	130	ND	13	100	95	80	Diff hypok, Ant, Ap dysk	Ant,	++
											Inf,	++
											PL,	0
											Ap	0
22	IVS	9′20″	Neg	135	ND	21.6	90	—	—	. . .	Ant,	0
											IVS	0
23	IVS	3′	Pos	150	Pos	22.5	. . .	. . .	. . .	. . .	Inf,	++
											IVS,	+
											Ap	+
24	IVS	12′	Pos	115	ND	18.4	. . .	. . .	. . .	. . .	Ant,	++
											IVS,	+
											Ap	0
25	Inf	9′30″	Neg	158	Neg	33.5	. . .	. . .	. . .	. . .	Inf	+
											Ap	+
26	Inf	3′30″	Neg	117	ND	18.7	. . .	. . .	. . .	. . .	Inf	+
27	Inf	6′30″	Neg	125	ND	25.0	. . .	. . .	. . .	. . .	Inf,	0
											PL,	0
											Ap	++

* Bridge.

Akin = akinesia; AL = anterolateral wall; Ant = anterior; Ap = apical; Bas = basal; Diff = diffuse; DMPI = delayed poststress myocardial perfusion imaging; DP = double product (systolic pressure × heart rate × 10^3); Dysk = dyskinesia; ECG = remote infarction site by electrocardiogram; EMPI = early poststress myocardial perfusion imaging; HR = maximal heart rate beats/min); Hypok = hypokinesia; Inf = inferior; IVS = interventricular septum; LAD = left anterior descending coronary artery; LBBB = left bundle branch block; LCx = left circumflex coronary artery; LV = left ventriculogram; MPI = myocardial perfusion imaging; ND = nondiagnostic; Neg = negative; NL = normal; PL = posterolateral; Pos = positive; RCA = right coronary artery; SE = subendocardial; ST = S-T segment depression. 0 = no redistribution; + = partial redistribution; ++ = complete redistribution; — = no lesions; . . . = not performed.

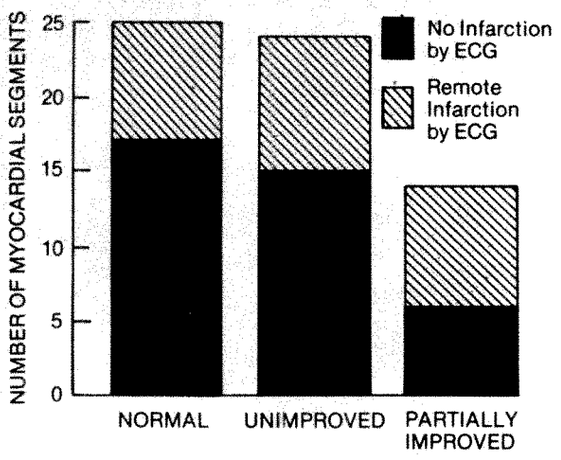


FIGURE 2. Redistribution of thallium-201 in 27 patients with prior infarction. There were 63 regions of abnormal perfusion in the early postexercise myocardial perfusion images. The graph depicts the findings in those regions in the delayed images.

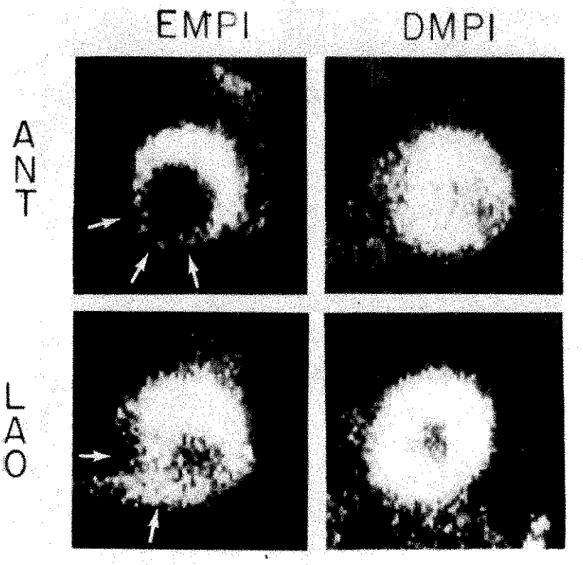


FIGURE 3. Case 2 (Group II). Thallium-201 redistribution in a patient with prior infarction. **Arrows** indicate decreased perfusion in the inferior and apical regions (**top left**), septum and inferior regions (**bottom left**). In the delayed myocardial perfusion images (DMPI), only a mild perfusion defect persists in the apex, the other regions have completely "filled in." The patient had prior inferior and anteroseptal infarction. ANT = anterior; EMPI = early postexercise myocardial perfusion image; LAO = left anterior oblique.

ratios in patients with and without infarction, in the early or late poststress scintigram. Table I also shows that perfusion ratios in both groups of patients improved substantially from the early to the late poststress scintigram. Visual interpretation of the early scintigrams in the total group of 27 patients demonstrated 63 regions with perfusion defects. Figure 2 illustrates the findings in these 63 regions in the delayed scintigrams: 25 of the 63 regions (40 percent) exhibited total redistribution, 14 (20 percent) demonstrated partial redistribution and 24 (38 percent) remained unchanged 4 to 6 hours after exercise. Figures 3 and 4 demonstrate the changes occurring from the early to the delayed scintigrams in patients with remote myocardial infarction.

Correlation of the site of necrosis and perfusion defects: Analysis of the 25 areas with electrocardiographic evidence of necrosis and corresponding perfusion defects in the immediate postexercise scintigram revealed that in the delayed images 8 of the 25 areas (32 percent) had total redistribution, 8 (32 percent) evidenced partial redistribution and 9 (36 percent) were unchanged (Fig. 3). Thus, approximately two thirds of electrocardiographic sites of myocardial infarction demonstrated complete or partial redistribution in delayed postexercise thallium-201 images. Among the 38 regions with decreased perfusion on immediate postexercise imaging that did not correspond to the electrocardiographic site of myocardial necrosis, 17 regions (45 percent) demonstrated total redistribution, 6 (16 percent) showed partial redistribution and 15 (39 percent) no change in the delayed images (Fig. 2). These values are similar ($P > 0.05$) to the redistribution patterns in regions with electrocardiographic evidence of infarction.

Thus, of the 27 patients with remote myocardial infarction, 100 percent evidenced one or more regions of decreased perfusion on immediate postexercise imaging. However, on delayed imaging, 5 (19 percent) demonstrated complete redistribution, 17 (62 percent) had partial redistribution and only 5 (19 percent) showed no redistribution. The abnormally perfused areas were also evaluated in each patient relative to the use of beta adrenergic blocking drugs and digitalis. Complete, partial and no redistribution, respectively, occurred in 43, 14 and 43 percent of areas in the presence of propranolol, in 25, 38 and 37 percent of areas in the presence of digitalis and in 43, 14 and 43 percent with combined propranolol and digitalis. In the remaining 15 patients receiving no cardiac medications, 41 percent demonstrated complete redistribution, 24 percent partial and 35 percent no redistribution. Thus, the redistribution patterns were similar ($P > 0.05$) with and without these cardiac medications.

Correlation with coronary arteriographic findings: In this group of 27 patients with prior myocardial infarction, ischemia was suggested by transient myocardial perfusion defects in 22 (81 percent). Of these 22 patients with evidence of ischemia, 16 (77 percent) underwent catheterization and 13 of these (77 percent) manifested stenosis of 50 percent or more of at least one coronary artery in addition to occlusion of the artery supplying the infarcted myocardium; in 4 patients ischemia occurred only in the area with preexisting infarction. Of the five remaining patients without evidence of transient perfusion defects, four had stenosis of additional coronary arteries. The extent and location of coronary stenoses did not relate closely to the redistribution pattern (Table II). In this regard it is note-

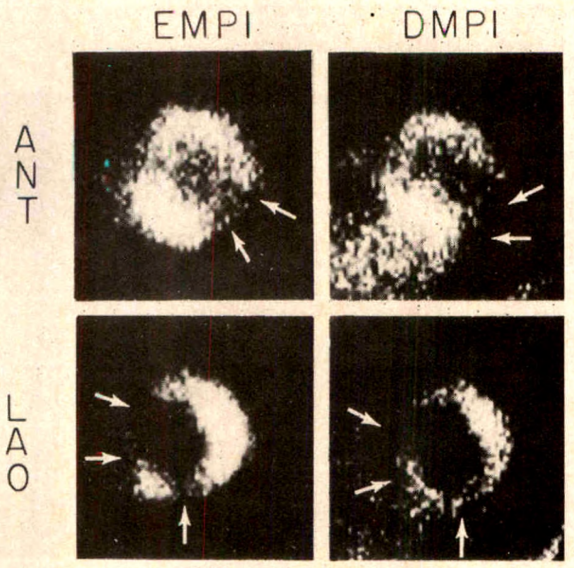


FIGURE 4. Case 13 (Group II). **Arrows** indicate decreased perfusion in the anterior apical wall (**top left**), septum and apex (**bottom left**) in the early postexercise myocardial perfusion images; the delayed images (DMPI) show no significant redistribution in the septum and only mild redistribution in the apex (**bottom right**). This patient had prior anterolateral infarction. Abbreviations as in Figure 3.

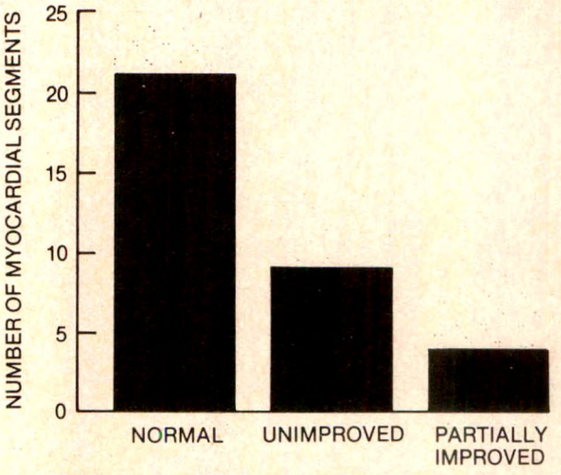


FIGURE 5. Redistribution of thallium-201 in 19 patients with coronary artery disease without prior infarction (Group III). There were 34 areas of decreased perfusion in the early postexercise myocardial perfusion image. The graph depicts the fate of those areas in the delayed images.

worthy that one, two and three vessel disease occurred with similar frequency among patients demonstrating complete redistribution.

Effect of coronary collateral vessels on thallium-201 redistribution: Seven of the eight zones corresponding to areas of myocardial necrosis without redistribution had, on arteriography, grade 0 or 1 (absent or poor) collateral vessels to the ischemic zone in question. In contrast, three of the four areas corresponding to the site of infarction but demonstrating normal early uptake of thallium-201 had grade 2 or 3 collateral vessels. Of all 21 zones with no redistribution, including 8 areas of infarction, 19 (90 percent) had no or poor collateral supply. In marked contrast, 9 of 12 areas (75 percent) perfused by collateral channels defined as good demonstrated complete redistribution, two showed partial redistribution and only one no redistribution.

Group III: Patients With Coronary Artery Disease Without Prior Myocardial Infarction:

Table III summarizes the results of treadmill stress testing, coronary arteriography and thallium-201 imaging in the 19 patients with coronary artery disease without prior myocardial infarction. Ischemic S-T segment depression occurred with exercise in 15 of the 19 patients (79 percent) in this group; 14 (74 percent) experienced angina pectoris and 17 (89 percent) had either ischemic S-T segment depression or angina with exercise. Nine patients were receiving propranolol and two were taking digitalis.

Regional perfusion ratios: Each patient had one or more regions demonstrating perfusion defects in the early scintigrams constituting a total of 34 areas of decreased perfusion (Table I). The mean perfusion ratios in each of the defined regions were reduced in the early scintigrams compared with those in normal subjects. On delayed imaging, 22 (65 percent) of the 34 abnormal regions demonstrated total redistribution, 3 (9 percent) had partial redistribution and 9 (26 percent) revealed no improvement (Fig. 5).

Among the nine patients receiving propranolol, complete, partial and no redistribution occurred in 73, 7 and 20 percent, respectively. Redistribution was complete in 63 percent, partial in 12 percent and absent in 25 percent of the eight patients receiving no cardiac medications. Thus, redistribution was not significantly ($P > 0.05$) altered by propranolol.

Of the 19 patients in this group, all with abnormal early thallium-201 images, 10 (53 percent) evidenced complete redistribution, 6 (31 percent) demonstrated partial redistribution and 3 (16 percent) had no change. Both early and delayed perfusion ratios tended to be higher in Group III than in Group II, but in no region was the difference statistically significant ($P > 0.05$). Additionally (Table I), with the exception of the anterior wall, all ratios in Group III normalized ($P > 0.05$ versus values in normal control subjects) with delayed perfusion imaging, indicating that substantial redistribution of thallium-201 had occurred. Figure 6 is an example of complete redistribution in the delayed scintigram; Figure 7 demonstrates an image with no delayed redistribution.

Correlation with location or extent of coronary stenoses on collateral channels: In this group, no clear relation was evident between the location or extent of the coronary stenoses and thallium-201 redistribution (Table III). Seven areas of myocardium in the distribution of totally occluded coronary arteries demonstrated normal early thallium uptake; six (86 percent)

TABLE III

Findings in 19 Patients With Coronary Artery Disease Without Prior Myocardial Infarction (Group III)

Case no.	Treadmill Stress Testing					Cineangiography				MPI	
	Time	Angina	HR	ST	DP	RCA	LAD	LCx	LV	EMPI	DMPI
1	3′30″	Pos	94	Pos	16.0	90	99	100	Diff hypok ap akin	Ap	+
2	10′15″	Pos	130	Pos	20.8	50	75	75	NL	Ant, PL	0 ++
3	11′	Pos	160	Pos	28.8	100	99	—	Inf bas hypok	Inf, IVS, Ap, Ant	++ ++ ++ ++
4	1′30″	Neg	125	Pos	22.5	100	90	80	Inf bas, ap hypok	Inf	++
5	6′	Pos	130	Pos	22.1	85	40	—	NL	Inf, IVS, Ap	++ ++ ++
6	6′	Neg	94	Pos	13.1	95	99	99	Diff hypok	Inf, IVS, Ap	++ 0 ++
7	8′	Pos	97	Pos	15.5	95	75	95	NL	PL	++
8	3′	Pos	128	Pos	17.9	100	80	80	Inf bas, ap hypok	Inf	0
9	7′20″	Pos	145	ND	29	100	90	90	Diff hypok	IVS, Ap	0 0
10	5′40″	Pos	124	Pos	16.1	75	—	—	Diff hypok, inf bas akin	Ap	0
11	4′15″	Pos	118	ND	16.5	100	—	—	Inf, ap hypok	PL	++
12	4′30″	Pos	128	Pos	24.3	—	70	—	NL	Ant, IVS	++ ++
13	6′40″	Neg	145	ND	29.5	...	...	...	...	IVS	++
14	5′	Pos	110	Pos	18.7	...	...	...	...	Inf, IVS, Ap	0 ++ 0
15	6′	Neg	95	ND	18	...	...	...	...	PL	++
16	7′40″	Pos	138	Pos	27.6	...	...	...	...	Ap	++
17	4′30″	Neg	167	Pos	26.7	...	...	...	...	Inf, IVS, Ap	0 ++ +
18	5′20″	Pos	140	Pos	21	...	...	...	...	PL	++
19	7′40″	Pos	140	Pos	23.8	...	...	...	...	IVS, Ap	++ +

Abbreviations as in Table II.

of these regions were supplied by grade 2 or 3 collateral channels.

Discussion

Correlation of ischemia on perfusion scintigraphy and prior myocardial infarction: In this investigation, which used a semi-quantitative technique of analysis, patients with prior myocardial infarction, manifested a high incidence rate (81 percent) of exercise-induced ischemia in thallium-201 perfusion scintigrams. In contrast, the exercise electrocardiograms demonstrated ischemic responses in only 42 percent of these patients. An additional 12 percent of patients with prior myocardial infarction experienced exercise-induced chest pain without electrocardiographic ischemic changes, so that 54 percent of the 27 patients had ischemic S-T segment depression or angina pectoris, or both. Of the areas with electrocardiographic prior myocardial infarction, most (76 percent) demonstrated perfusion abnormalities in the early postexercise scintigrams. Exercise-induced ischemia, evidenced by complete or partial redistribution in the delayed postexercise image, occurred in the region of the infarction in the majority of patients (62 percent) with prior myocardial infarction; that is, most immediate postexercise filling defects corresponding to electrocardiographic infarctions exhibited partial or total filling-in on delayed imaging. Thus, the majority of areas of remote myocardial necrosis do not behave in a static manner relative to thallium-201 distribution on immediate and delayed poststress myocardial perfusion imaging. These findings indicate that periinfarction ischemia commonly occurs with chronic infarction and, moreover, that still other areas of prior necrosis apparently reestablish vascularity sufficient to afford total redistribution of thallium-201 on delayed postexercise imaging.

Controversy persists concerning the need for resting scintigrams in addition to the delayed postexercise image.[5,8,9] Our data indicate that 32 percent of anatomic areas corresponding to the electrocardiographic site of infarction and 19 percent of patients with myocardial infarction by electrocardiographic criteria may demonstrate complete redistribution by 6 hours. Moreover, perfusion defects persisting at 6 hours after exercise may represent either markedly delayed redistribution or true scar related to previous myocardial infarction. In this regard it was recently reported[8] that 46 percent of patients with electrocardiographic criteria for myocardial infarction demonstrate normal thallium perfusion at rest, and only 7 percent manifest complete early redistribution. This discrepancy of 39 percent would appear to justify frequent acquisition of the resting scintigram, particularly when a clinical decision re-

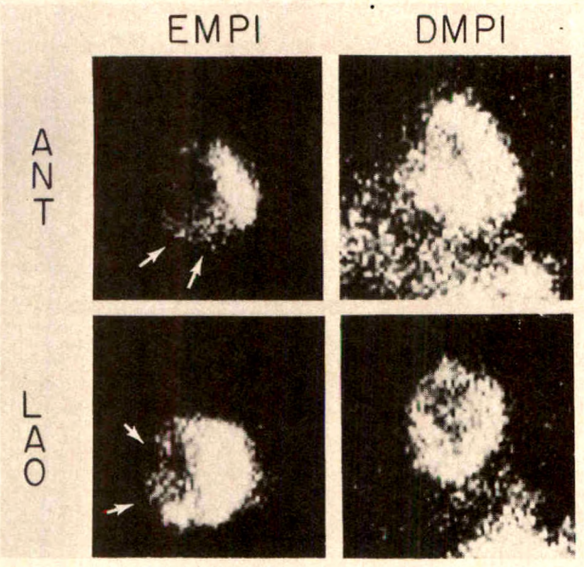


FIGURE 6. Case 3 (Group III). Thallium-201 redistribution in a patient with coronary artery disease without remote infarction. **Arrows** indicate decreased perfusion in the inferior wall (**top left**) and septum (**bottom left**). There is complete redistribution in the delayed images. Abbreviations as in Figure 3.

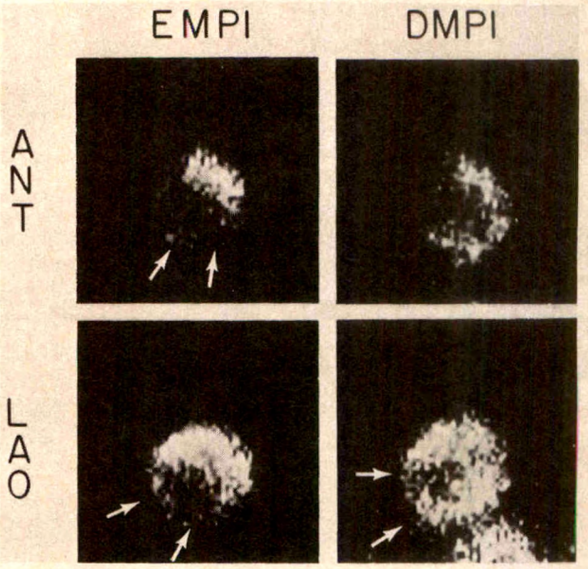


FIGURE 7. Case 6 (Group III). Thallium-201 redistribution in a patient with coronary artery disease without prior infarction. **Arrows** indicate decreased perfusion in the inferior wall and apex (**top left**) and septum (**bottom left**); there is complete redistribution in the inferior wall and apex and no redistribution in the septum in the delayed myocardial perfusion images. Abbreviations as in Figure 3.

garding the feasibility of surgical revascularization is entertained. An additional possibility, not yet examined, is that a redistribution scan obtained 8 to 12 hours after the first study may provide further discrimination.

Mueller et al.[12] demonstrated that the mass of an area of experimental myocardial infarction must be greater than 4.9 g in order to be detected with scintigraphy. Additionally, Wackers et al.[13] demonstrated that the number of false negative perfusion images in patients with acute myocardial infarction is directly related to the time interval from the acute event to the scintigram, suggesting that in certain instances the final size of the infarct may be too small to be detected by imaging. Furthermore, our findings suggest that in some cases even areas of previous segmental necrosis may have the potential to benefit from coronary bypass if accentuation of the perfusion defects is demonstrated to occur with stress. We[14,15] have previously shown that this is indeed the case in selected patients undergoing myocardial revascularization.

Myocardial hypoperfusion at sites other than that of prior myocardial infarction: An additional important finding in this investigation was that thallium-201 imaging identified transient myocardial hypoperfusion in sites other than the site of the infarct in 59 percent of the patients with prior infarction. However, ischemia occurred in areas contiguous with the site of prior infarction in nine patients, such as in the interventricular septum with anterior infarction and in the apex with either anterior or inferior infarction. Those areas contiguous with the site of prior infarction were considered involved as a result of occlusion of the same vessel that caused the prior infarction and therefore could not predict involvement of additional vessels. With exclusion of these contiguous areas, postexercise perfusion imaging detected perfusion defects in areas unrelated to infarction in 47 percent of patients with prior myocardial necrosis and multivessel coronary artery disease.

Postexercise scintigram versus electrocardiogram: We have previously demonstrated the wide prevalence of multivessel coronary artery disease in patients with recent uncomplicated inferior myocardial infarction as well as the difficulty in predicting this finding noninvasively.[16] Finally, the decreased sensitivity of the exercise electrocardiogram in detecting ischemia in patients with prior infarction has previously been noted.[17–19] The present study confirms the decreased sensitivity of the stress electrocardiogram in identifying ischemia and indicates that postexercise immediate and delayed perfusion images are superior to the stress electrocardiogram ($P < 0.05$) in detecting ischemia in the presence of prior myocardial necrosis.

Persistent perfusion abnormality without prior myocardial infarction: Although the majority of immediate postexercise perfusion abnormalities in patients without prior infarction demonstrated partial or total redistribution on delayed imaging, a substantial number of patients evidenced no redistribution. The explanation for this persistent filling defect in the absence of previous myocardial necrosis or fibrosis is unknown. It is possible that in some instances, complete redistribution would have occurred had delayed scintigrams been obtained after an even longer interval. It is also possible that certain of the persistent defects did

in fact represent myocardial fibrosis consequent to healed infarctions not detected in the resting electrocardiogram. The disappearance of diagnostic Q waves in the resting electrocardiogram after myocardial infarction, particularly of the inferior wall, has been well described.[20–23] However, in the present investigation, none of the patients in Group III had a history or prior documentation of infarction.

Effect of coronary collateral vessels: This investigation suggests a close relation between angiographically documented collateral vessels to an ischemic zone and total redistribution of the area. On the other hand, almost all hypoperfused regions corresponding to totally occluded coronary arteries with no or poor collateral vessels failed to demonstrate complete redistribution. Thus, it appears that good quality collateral vessels may be inadequate to augment myocardial blood flow distal to a stenosis of a major coronary artery during stress, even though they afford relatively normal resting myocardial perfusion to the same region and thereby allow total redistribution. A similar beneficial effect of the coronary collateral vessels on resting but not exercise myocardial perfusion has been described by Berman et al.[24] However, the effect of the collateral vessels on thallium-201 distribution has not previously been evaluated.

Acknowledgment

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Infection of Glutaraldehyde-Preserved Porcine Valve Heterografts

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Gross, histologic and ultrastructural changes associated with bacterial infection are described in four porcine valve heterografts that had been in place in patients for 6 days to 28 months. In one patient, culture of the aortic tissue tag included in the heterograft container grew Mycobacterium chelonei; however, examination of the heterograft, recovered at necropsy 6 days after implantation, revealed small colonies of bacteria that differed morphologically from mycobacteria. A second heterograft was the site of staphylococcal infection associated with extensive destruction of collagen in the leaflets. Similar destruction was observed in a third heterograft, which was found to have organisms on ultrastructural study even though bacterial cultures of the valve were negative. The fourth heterograft, from a patient who died of coronary embolism secondary to dislodgment of vegetative material, contained structures resembling lysed bacteria. Observations in these 4 patients and review of published reports of infection involving 43 other patients with porcine valve heterografts indicates that infection in these valves: (1) develops in the fibrin layer that covers the cusps, (2) can involve the collagen in the leaflets, and (3) is uncommonly (three patients) associated with valve ring abscesses.

Infection of a valve prosthesis is a serious complication of cardiac valve replacement. Detailed descriptions have been made of the clinical and morphologic features of infections in rigid-framed prosthetic valves[1–18]; however, only a few reports have been published of infections in glutaraldehyde-preserved porcine valve heterografts,[19–32] and morphologic changes associated with these infections have received little attention. This communication describes gross, histologic and ultrastructural alterations associated with bacterial infection in four porcine valve heterografts, summarizes previous reports of infection in porcine heterografts and compares the features of infections in these valves and in other types of prosthetic heart valves.

Methods

Patients Studied

The study group consisted of four patients, three men and one woman, aged 28 to 68 years (average 50), who had bacterial infection in a glutaraldehyde-treated porcine valve heterograft. Evidence of infection was obtained from bacterial culture or morphologic examination of the prosthesis, or both. The clinical features of these four patients and the morphologic features of the heterografts are summarized in Tables I and II.

The porcine valve heterografts had been in place for 6 days to 28 months. In Patient 1, the heterograft was implanted in the aortic position. Patient 2 had two heterografts, one in the aortic and one in the mitral position; the latter heterograft did not become infected. Patient 3 also had two heterografts, one in the mitral and one in the tricuspid position; only the mitral heterograft became infected. In Patient 4, the heterograft was in the mitral position.

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TABLE I

Clinical Findings in Four Patients With Infected Porcine Valve Heterografts

Clinical Features	Patient 1	Patient 2	Patient 3	Patient 4
Age (yr)	66	68	28	44
Sex	F	M	M	M
Preop diagnosis	AR, aortic aneurysm	AR, MR	MR, TR	MR
Valve replaced with PVH	Aortic	Aortic and mitral	Mitral and tricuspid	Mitral
Factors predisposing to infection	0	0	Opiate addiction	0
Cultured organism	Mycobacterium chelonei cultured from tag	Enterobacter cloacae, α-Streptococcus, Citrobacter fuente	Staphylococcus aureus	None
Clinical evidence of PVH infection	0	Suggestive	+	Suggestive
Noncardiac infection	0	0	+	0
Antibiotic therapy before PVH excised	0	0	Nafcillin for 6 weeks	0
PVH dysfunction	0	+ (stenosis)	+ (stenosis)	+ (stenosis)
Interval between PVH implantation and removal	6 days	5 months	4.5 months	28 months
Outcome	Died of ascending aortic aneurysm	Died of coronary embolus	Alive; infected mitral PVH replaced with another PVH	Alive; PVH replaced with rigid-framed valve

+ = change present; 0 = change absent; α-Streptococcus = alpha-hemolytic streptococcus. AR = aortic regurgitation; MR = mitral regurgitation; preop = preoperative; PVH = porcine valve heterograft; TR = tricuspid regurgitation; TVR = tricuspid valve replacement.

Case Reports

Patient 1, who had a diagnosis of aortic regurgitation secondary to the Ehler-Danlos syndrome, died of complications of dissecting aneurysm 6 days after implantation of the aortic porcine valve heterograft. She had no clinical evidence of infection of the heterograft, but a tag of aortic tissue included in the heterograft container was cultured at the time of operation and eventually grew Mycobacterium chelonei.[33,34] At necropsy, the heterograft appeared grossly normal and was not cultured.

Patient 2, who had been hospitalized in 1974 for suspected (unproved, but treated) infective endocarditis, was admitted in August 1977 with congestive heart failure secondary to aortic and mitral regurgitation. The mitral and aortic valves were replaced by porcine valve heterografts. Two days after operation, the patient had an episode of atrial fibrillation, and expressive aphasia and right-sided hemiplegia developed. He was discharged several weeks later without further complications but, in January 1978, he died of a coronary embolus 1 day after admission for treatment of recurrent congestive heart failure. At necropsy, the cusps of the aortic heterograft were filled with abundant vegetations.

Patient 3, an opiate addict who had used drugs intravenously for about 10 years, had severe mitral and tricuspid valve regurgitation after three separate episodes of infective endocarditis (two with Staphylococcus aureus and one with alpha streptococcus). In August 1977, he underwent mitral and tricuspid valve replacement with porcine valve heterografts. The excised valves showed evidence of healed endocarditis, but no organisms were detected on culture or histologic study. One week after operation, complete heart block developed, requiring implantation of a permanent epicardial pacemaker. In November 1977, the patient was admitted with a Staphylococcus aureus infection involving the mitral valve heterograft and the site of implantation of the pacemaker batteries. The patient responded to removal (and replacement) of the pacemaker and to therapy with nafcillin; however, in January 1978, less than 2 weeks after discharge, he was again admitted with evidence of staphylococcal infection of the mitral valve heterograft. Because of the persistence of symptoms and echocardiographic findings suggestive of vegetations, this heterograft was replaced by another porcine valve. At operation the other cardiac valves, including the tricuspid porcine heterograft, were normal. The mitral valve

TABLE II

Morphologic Observations on Four Infected Porcine Valve Heterografts

Case no.	Gross Appearance of Cusps	Microscopic Changes: Fibrin	Inflammatory Cells	Disrupted Collagen	Calcific Deposits	Lipid Deposits	Organisms
1	Normal	+	0	+	0	0	Rods with flagella; located beneath thin fibrin layer covering surface
2	Friable tan-yellow vegetations narrowing valve orifice	+	+	++	0	0	Rounded "ghosts", not definitely identifiable as bacteria, in vegetations
3	Vegetations; valve orifice narrowed	+++	+	+++	+	++	Cocci in cusps and vegetations
4	Covered with thick shaggy material	++	+	+++	+	+++	Spore-forming, rod-like bacteria in cusps

0 = none; + = mild; ++ = moderate; +++ = severe.

heterograft contained multiple vegetations with gram-positive cocci. A small pocket of pus was present in the valve ring and grew Staphylococcus aureus in culture. The patient has done well since operation.

Patient 4 (Patient 10 in reference 35) had a history of an "autoimmune disease" characterized by vasculitis, arthritis and temporal arteritis. In 1974, because of mitral regurgitation caused by rupture of chordae tendineae, he underwent mitral valve replacement with a porcine valve heterograft. In June 1976, congestive heart failure developed; a mean diastolic pressure gradient of 34 mm Hg across the porcine mitral valve was recorded. The white blood cell count was 16,500/mm^3 of blood, but, no antibiotic treatment was given before reoperation because results of blood cultures were negative and there were no embolic signs or fever. At reoperation, the porcine valve appeared to be partially disintegrated and was covered with a large amount of shaggy gray friable material. The heterograft was replaced by a rigid-framed prosthesis, and the patient recovered uneventfully.

Preparation of Tissues

The porcine valve heterografts were removed either at operation (Patients 3 and 4) or at necropsy (Patients 1 and 2) and were fixed with cold 3 percent glutaraldehyde in 0.1 molar phosphate buffer, pH 7.2. Histologic sections were prepared according to techniques reported previously in detail.[35] Selected portions of the valves were cut, fixed with cold 1 percent osmium tetroxide in Millonig's phosphate buffer, and embedded in Maraglas®.[35] Sections, 0.5 μ thick, were stained with alkaline toluidine blue and examined with a light microscope to select areas for electron microscopic study. Ultrathin sections were stained with ethanolic uranyl acetate and Reynolds' lead citrate, and examined with a JEOL 100B electron microscope.

Results

The results of gross anatomic, histologic and ultrastructural examination of the four valves are summarized in Table II.

Patient 1: The porcine valve was grossly normal. Microscopically, it showed only minimal disruption of collagen and a few small (less than 20 μ in size) colonies of bacteria. The bacteria (Fig. 1) were located in a thin layer of fibrin that covered the heterograft and between this layer and the surface of the heterograft. They were not observed in deeper areas of tissue, were not associated with inflammatory cells and were not acid-fast. On ultrastructural examination (Fig. 2), the morphologic features of the bacteria corresponded to those of flagella-bearing gram-negative rods. These organisms appeared well preserved and could have been viable. The bacteria had thin cell walls and well defined trilaminar membranes. The cytoplasm of the bacteria contained abundant clusters of electron-dense granules scattered between clumps of nucleoid material. The bacteria had an average length of 2 μ and width of 0.5 μ.

Patient 2: The cusps of the porcine valve contained abundant friable yellow-tan vegetations that severely narrowed the valve orifice. Microscopically, the vegetations consisted of laminated masses of fibrin in which a few neutrophils and macrophages were present (Fig. 3, A to C). Special stains of histologic sections revealed no organisms; however, light and electron microscopic examination of plastic-embedded fragments of vegetations revealed the presence of rare foci of rounded or somewhat elongated structures that measured about 0.4 μ in diameter. These ghost-like structures had fragmented trilaminar membranes and dense, poorly defined contents (Fig. 3, D and E).

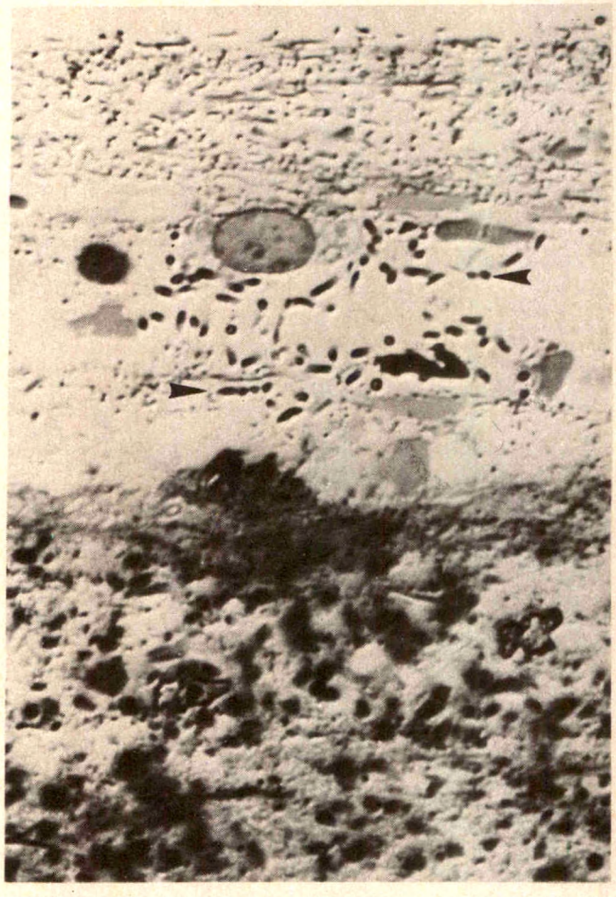


FIGURE 1. Patient 1. Light micrograph of section of the heterograft. A thin layer of fibrin overlies the surface of the heterograft, and a small cluster of bacteria (**arrowheads**) is located between the fibrin and the valve collagen. Section of plastic embedded tissue, 0.5 μ thick, stained with toluidine blue and viewed with Nomarski differential interference contrast optics (×1,600, reduced by 5 percent).

Patients 3 and 4: The valves from these two patients had extensive vegetations on the cusps. Although these valves demonstrated different organisms, they showed very similar ultrastructural changes, including severe disruption of the collagenous framework, lipid deposits and focal calcific deposits. The changes in collagen and the lipid deposits were similar to those previously described in deteriorating porcine valve heterografts.[35] The calcific deposits were present in fibrin-platelet thrombi. In addition, both valves had sites of deep penetration by bacteria into the substance of the leaflets. In contrast, polymorphonuclear leukocytes and macrophages were located mostly in the vegetations. In both valves, these cells were present only in small numbers on the surfaces of the leaflets and were essentially absent from the deep-seated areas of bacterial invasion.

In Patient 3 the bacteria in the porcine valve heterograft were readily identified as cocci on light microscopic study of histologic sections and plastic sections of tissue embedded for electron microscopy (Fig. 4). On ultrastructural study, these organisms appeared round in shape, measured up to 1.2 μ in diameter and had prominent cell walls, discrete plasma membranes, mesosomes and filamentous strands of nuclear material (Fig. 5). These ultrastructural features are known to

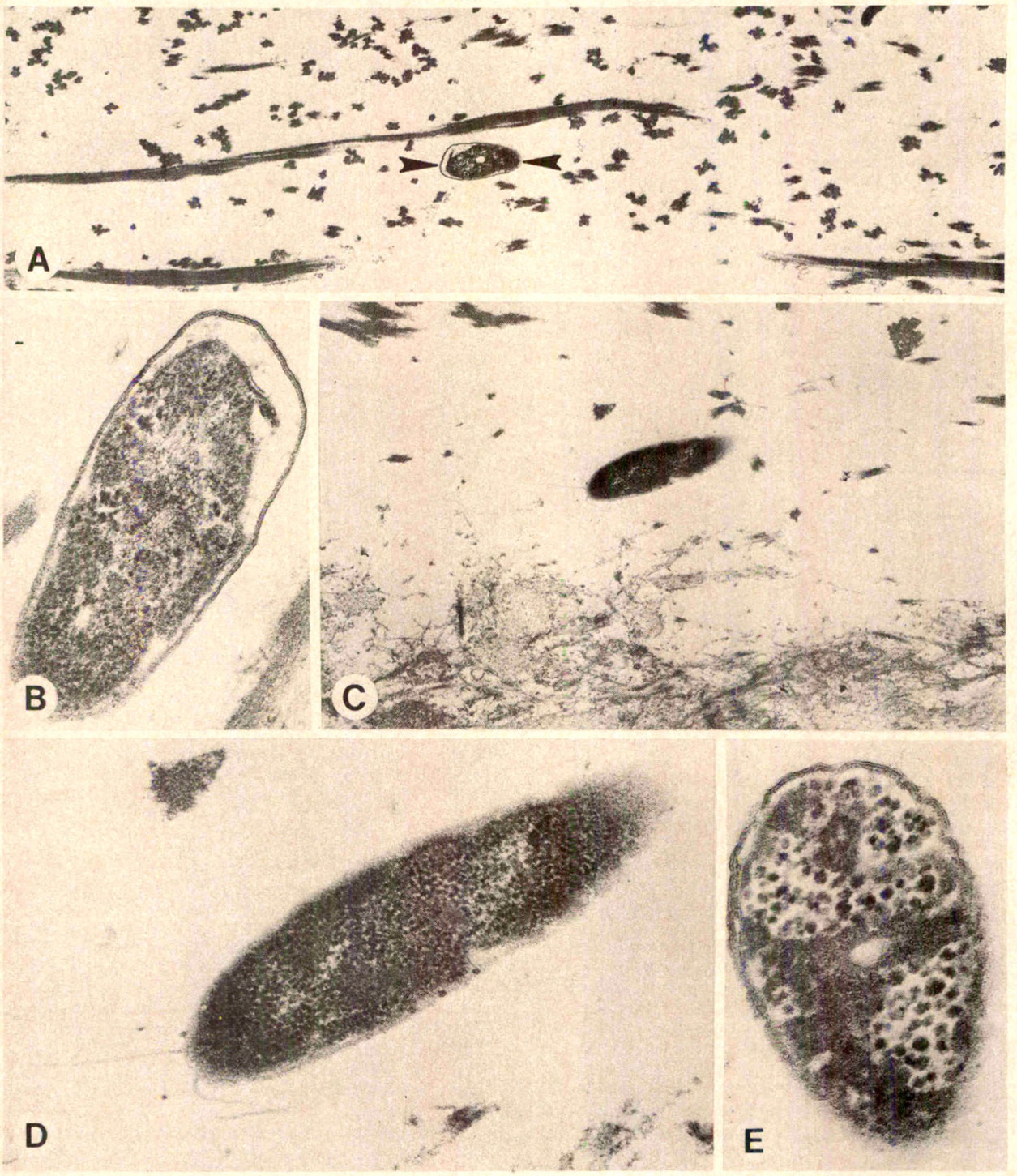


FIGURE 2. Patient 1. Electron micrographs showing the morphologic features of bacteria in the heterograft (all specified magnifications reduced by 2 percent). **A,** low magnification view of bacterium (**arrowheads**) surrounded by thin, elongated strands of fibrin (×14,600); **B,** bacterium from a section serial to that shown in **A** has trilaminar plasma membrane and a very thin cell wall of the type found in gram-negative bacteria (×66,500); **C,** another bacterium is immediately adjacent to layer of altered collagen at the surface of the heterograft (**bottom**). Fibrin strands are shown at **top** (×19,700); **D,** high magnification view of the same bacterium as in **C,** showing flagella (**lower left**) (×61,500); **E,** slightly oblique section through another bacterium showing the good preservation of its cytologic features. Note the plasma membrane and the thin cell wall (×75,000).

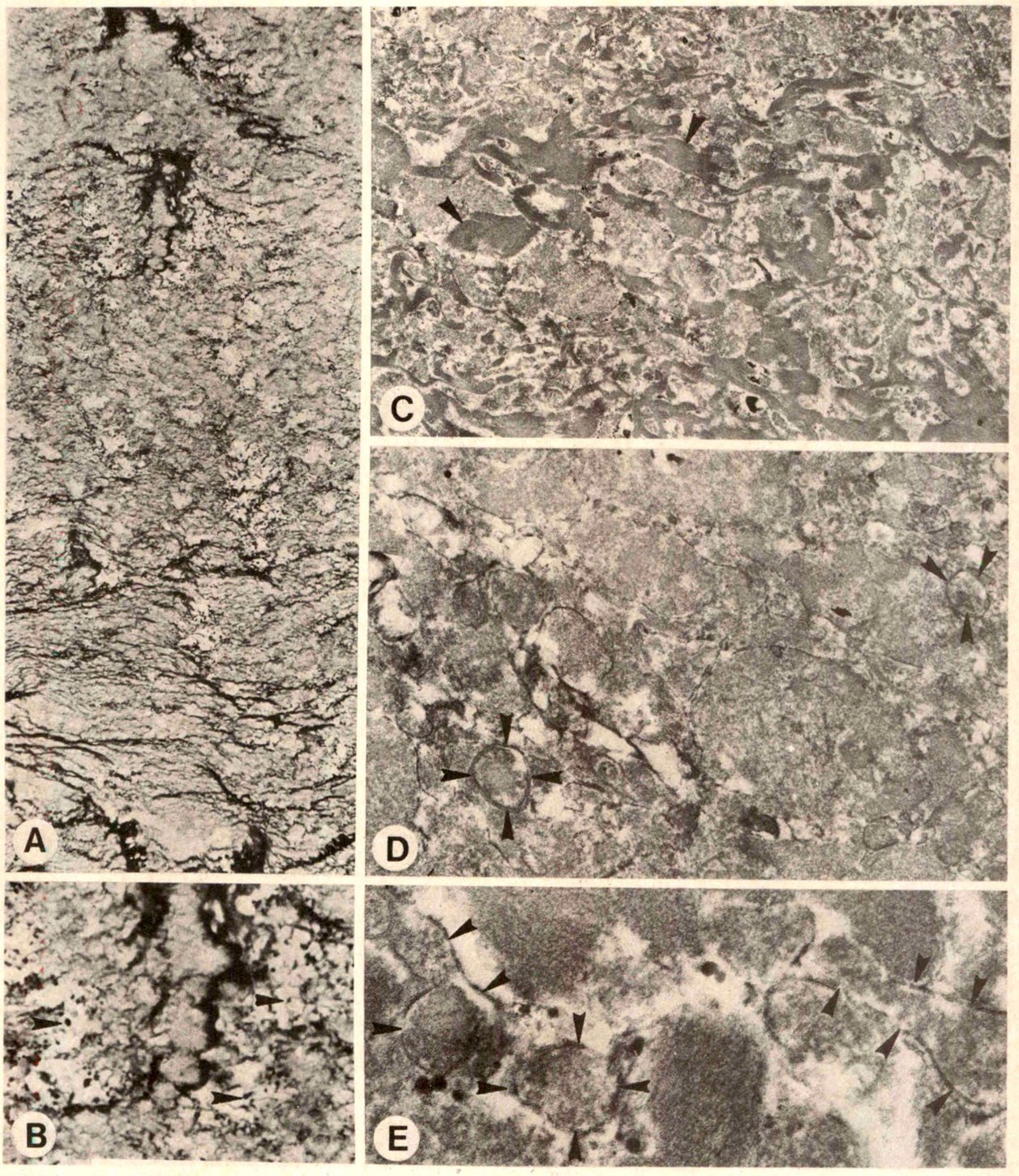


FIGURE 3. Patient 2. Light (**A** and **B**) and electron (**C, D** and **E**) micrographs of sections through large vegetation on cusp of heterograft. (all specified magnifications reduced by 2 percent). **A,** vegetation is composed of layered strands of fibrin. Section, 0.5 μ thick, toluidine blue stain (×250); **B,** Small rounded or slightly elongated particles (**arrowheads**) are present in close association with the fibrin. Section, 0.5 μ thick, toluidine blue stain (×800); **C,** low magnification electron micrograph of fibrin strands (**arrowheads**) in the vegetation (×12,000); **D,** "ghost-like" forms (**arrowheads**) resembling bacteria are present in an area similar to that shown in **B** (×34,000); **E,** high magnification view of structures (outlined by **arrowheads**) such as those shown in **D.** The gray material surrounding these structures is fibrin (×75,000).

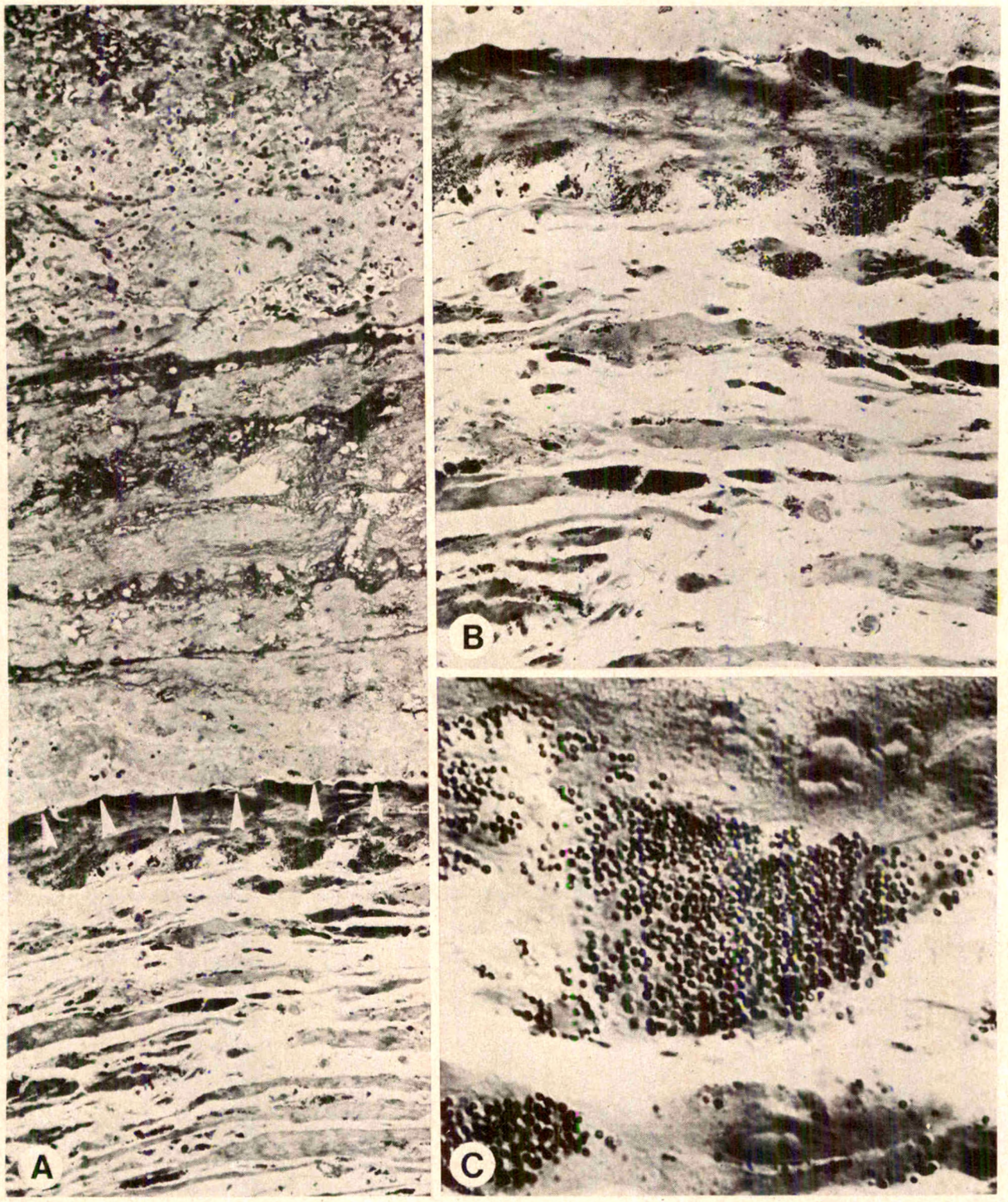


FIGURE 4. Patient 3. Light micrographs of sections, 0.5 μ thick, stained with toluidine blue, of valve heterograft (all specified magnifications reduced by 7 percent). **A**, low magnification view of large vegetation (**top** and **center**) overlying valve surface (indicated by **small white arrowheads**) and valve fibrosa. Vegetation contains layered fibrin and inflammatory cells (×200); (**B**, view of valve heterograft (corresponding to lower third of **A**) showing bacterial invasion of collagen bundles, which appear widely separated. Note the absence of inflammatory cells from this area of the heterograft (×400); **C**, high magnification micrograph (Nomarski differential interference contrast optics) of cluster of bacteria (same cluster as in upper right of **B**) having the typical morphologic features of cocci (compare with Fig. 5) (×1,600).

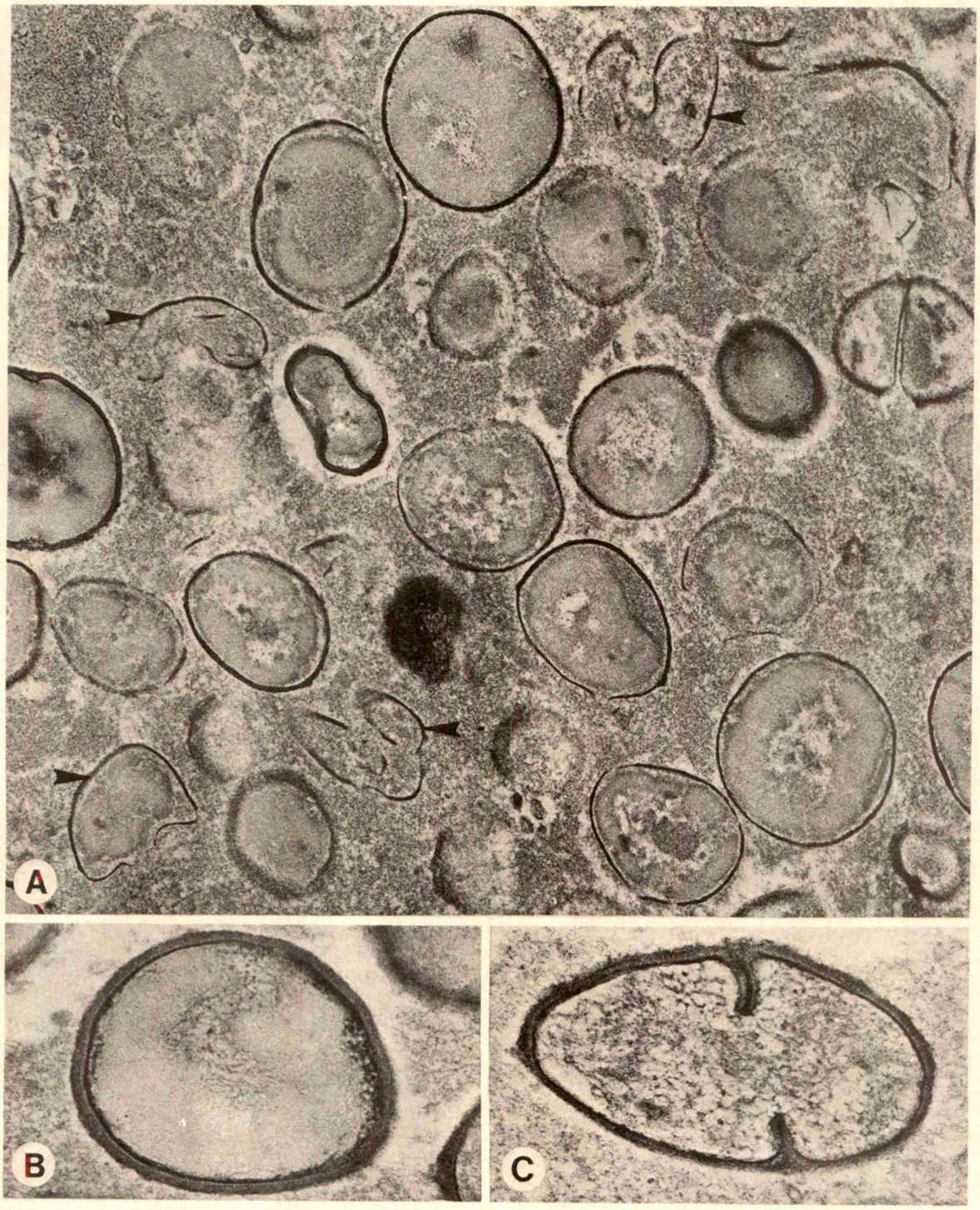


FIGURE 5. Patient 3. Electron micrographs of staphylococci in vegetations on the heterograft (all specified magnifications reduced by 9 percent). **A,** numerous closely packed organisms are embedded in amorphous material. Note that several of these bacteria have disrupted cell walls (**arrowheads**) and appear to have lysed (×35,400); **B,** intact bacterium with thick cell wall and pale-staining fibrillar nuclear material (×84,000); **C,** organism that is in process of dividing, as evidenced by partial formation of new septum composed of cell membrane and cell wall (×94,000).

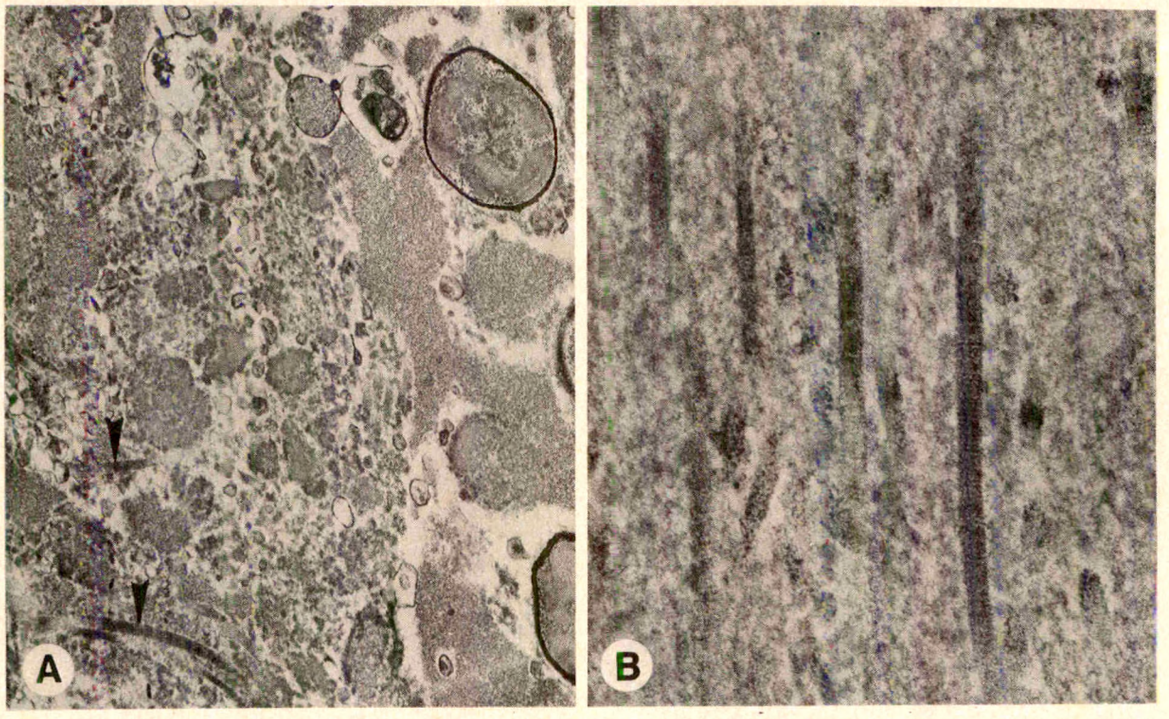


FIGURE 6. Patient 3. Electron micrographs of valve damage in heterograft (all specified in magnifications reduced by 10 percent). **A,** area of invasion of valve collagen by staphylococci (**upper right**). Note the severe disorganization of collagen structure (a few remaining collagen fibrils are indicated by **arrowheads**) and the accumulation of considerable amount of debris (×30,000); **B,** high magnification view of area similar to that in lower left of **A.** Only a few collagen fibrils are recognizable, and they are surrounded by gray material presumed to be necrotic collagen (×85,000).

be typical of staphylococci.[36–38] Many organisms appeared to be in different stages of lysis and nucleoid disintegration. Others showed evidence of continuing cell division, as manifested by the presence of partially developed cell walls. The cell walls in numerous bacteria were thinner than normal. Such cells were lysed and were in the process of extruding their content. The bacteria that had penetrated the deepest into the collagen framework of the cusps showed the least morphologic change. Many of these bacteria still had a normal cell wall structure, with outer and inner dense layers and an intervening less dense layer. Their cell walls also varied in thickness. The collagen bundles that had been invaded by bacteria were fragmented, disrupted and necrotic (Fig. 6).

In Patient 4 the valve was shaggy and necrotic. Bacteria in this valve were not identifiable on light microscopic study using special stains, but ultrastructural examination revealed a number of colonies of spore-forming rod-like bacilli measuring up to 1.5 μ in length and 0.3 μ in width. The appearance of these bacteria was variable (Fig. 7). Some organisms consisted mainly of empty shells and appeared dead; others were well preserved and could have been viable. The organisms present deep in the substance of the cusps were associated with severely necrotic connective tissue. As in the valve of Patient 3, inflammatory cells were present in the vegetations on the surface of the heterograft, but did not penetrate into the underlying collagen framework.

Discussion

Morphologic features of infection of porcine valve heterografts: The morphologic observations in these four patients illustrate the variety of clinical and morphologic changes associated with infection of porcine valve heterografts.

The findings in Patient 1 are compatible with a very early infection of a recently implanted (6 days) heterograft. This situation is complicated by the finding of two different organisms, one demonstrated morphologically in the valve itself and the other grown on culture of the aortic tissue tag. This infection was clinically inapparent, as would be expected in a valve that had only a few small colonies of bacteria. The excellent state of preservation of these organisms suggests that they were viable and probably had not been present at implantation of the valve (perhaps colonizing it before commercial processing) and then inactivated by treatment of the valve with glutaraldehyde before clinical use. However, the latter possibility cannot be excluded because it is known that porcine valves are collected under nonsterile conditions at the time when the animals are killed and that they are sterilized by the glutaraldehyde processing. In this respect, it must be noted that Ashraf and Bloor[39] reported the detection, using scanning electron microscopy, of elongated, rod-like bacteria on the surface of a porcine heterograft that had been in place in the aortic position for 2 months in a patient with a previous history of aortic regurgitation secondary to staphylococcal endocarditis. The clinical significance of the rod-like bacteria they found in this valve at necropsy is uncertain. The organisms found in our Patient 1 were located deep to the layer of fibrin

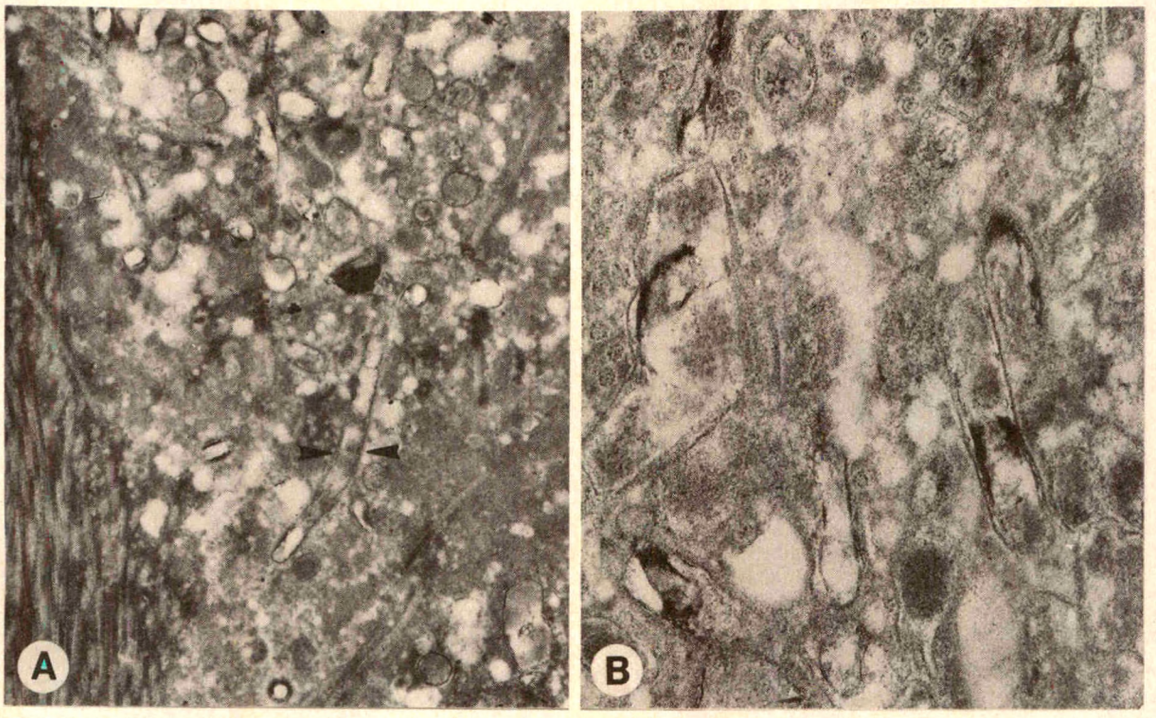


FIGURE 7. Patient 4. Electron micrographs of bacteria in heterograft (all specified magnifications reduced by 10 percent). **A,** low magnification view of colony of elongated, rod-like bacteria (**arrowheads**) deep in leaftlet of heterograft. Note the bundle of collagen fibrils at **lower left** and amorphous, dark gray material surrounding the bacteria. The round clear spaces represent lipid deposits (×22,500). **B,** the bacteria are surrounded in collagen and amorphous material. Some of the organisms have electron-dense lamellae in their cytoplasm (×45,000).

covering the surface of the heterograft, suggesting that they were not postmortem contaminants. Accordingly, we favor the possibility that these organisms represented an early stage of infection that would have become clinically manifest had the patient survived longer.

The species of the organism detected on ultrastructural study of the heterograft from Patient 1 could not be determined on the basis of morphologic study alone. Nevertheless, our observations show that the morphologic features of this organism differed from those of the Mycobacterium chelonei that grew on culture of an aortic tissue tag included in the container of the heterograft implanted in this patient.[33,34] The bacteria observed by us had flagella and thin cell walls. In contrast, mycobacteria are nonmobile and lack flagella; they have thick complex cell walls in which the mycobacterial waxes (responsible for acid-fastness) are present.[40–42] Thus, it is tempting to conclude that the heterograft from Patient 1 was infected with two different organisms. Among the patients reported to have received porcine valve heterografts from which the aortic tags grew Mycobacterium species in culture, only one[34] had clinical evidence of infection with this type of organism. This patient had pericardial effusion 2 months after valve implantation, and Mycobacterium chelonei was cultured from the pericardial fluid. We are aware of only one patient who had infection with Mycobacterium chelonei in a prosthetic heart valve.[43] This patient underwent aortic valve replacement with a Björk-Shiley valve because of endocarditis due to gram-positive cocci. Four and one-half months after operation, fever and aneurysmal dilatation of the ascending aorta developed. Blood cultures grew Mycobacterium chelonei. The patient died of rupture of the aneurysm, and at necropsy vegetations containing acid-fast bacilli (again shown by culture to be Mycobacterium chelonei) were found attached to the edge of the prosthesis and on the aortic incision line.

Patients 2 and 4 illustrate other problems encountered in the bacteriologic diagnosis of infections of porcine valve heterografts. Although Patient 2 had large florid vegetations filling the cusps and obstructing the orifice of this aortic porcine heterograft, and his death was caused by a coronary embolus, incontrovertible evidence of prosthetic infection could not be obtained. Culture of heart blood at necropsy grew three different organisms (alpha-streptococcus, Enterobacter cloacae, Citrobacter fuente), which were considered likely to be contaminants. Electron microscopic examination of the vegetations disclosed "ghost" forms that resembled bacteria but could not be unequivocally identified as such. These forms differed from the cell wall-deficient bacteria recently reported by Piepkorn and Reichenbach[44] to cause endocarditis involving native valves in four patients.

The nature of the infection in Patient 4 also remains uncertain because no growth was obtained on culture

TABLE III

Reports of Infection of Implanted Porcine Valve Heterografts

Author (Reference)	no. of PVH in Study	no. (%) of Inf. PVH (incidence)	Site of Inf. PVH	Time Bet. Impl. and Infection (mo)	Infecting Organism	Predisposing Factor	Total Patients With: PVH Sten.	PVH Reg.	Ring Abcess	PVH Leaf. Perf.	Perivalve Leak	Death Related to Infection
Zuhdi et al.[19]	137	1 (0.7)	A	>4.5	—	—	0	0	0	0	1	1
Carpentier et al.[20]	116	3 (2.6)	A	>12	—	—	—	—	—	—	—	1
			M	>2	—	—	—	—	—	—	—	1
			T	—	—	—	—	—	—	—	—	0
Horowitz et al.[21]	32	1* (3.1)	M	—	Strept	GU infection	0	0	0	0	0	0
McIntosh et al.[22]	136	5 (3.7)	A-V	2 valves <1	—	—	0	—	—	—	—	2
			A-V	3 valves >1	—	—	0	—	—	—	—	3
Buch et al.[23]	120	1 (0.8)	M	20	Enterococcus	Dental manipulation	—	0	—	—	—	0
Pipkin et al.[24]	75	1* (1.3)	A	39	—	—	—	1	—	—	—	1
Cohn et al.[25]	—	2 (—)	—	—	—	—	—	—	—	—	—	1
Stinson et al.[26]	218	1 (0.5)	A	—	—	—	—	1	—	—	—	1
	294	1 (0.3)	M	—	—	—	—	1	—	—	—	1
Gallucci[27]	387	3 (0.8)	—	—	—	—	—	—	—	—	—	—
Fishbein et al.[28]	363	4 (1.1)	A	31	α-Strept.	—	—	1	—	—	—	0
			M	12	Candida paropsilosis	—	—	1	—	—	—	0
			M	1.2	Pseudomonas aeruginosa	—	—	—	—	—	—	1
			A	0.5	Phycomyces	—	1	0	0	0	0	1
Moseley et al.[29]	1	1 (—)	P	0.5	Enterobacter Staph. epidermidis	—	0	0	0	0	0	0
Oyer et al.[30]	339	5 (1.5)	A	—	—	—	—	—	—	—	—	1
	426	1 (0.2)	M	—	—	—	—	—	—	—	—	1
Magilligan et al.[31]	470	11 (2.3)	A-V	32	Strept. faecalis	Opiate addict	—	0	—	—	—	0
			A	12	α-Strept.	—	0	1	1 (S)	0	0	1
			A	3	α-Strept.; Staph. epidermidis; H. influenzae	Opiate addict	0	0	0	0	0	0
			M	21	Enterobacter cloacae	—	—	0	—	—	—	0
			M	24	Strept. faecalis	—	0	0	0	0	0	0
			M	6	α-strept.	Opiate addict	—	0	—	—	—	0
			A	29	α-strept.	Dental extraction	0	1	1 (S)	0	0	1
			M	7	α-strept.	Opiate addict	0	0	0	0	0	0
			M	45	Strept. faecalis	—	—	0	—	—	—	0
			—	36	Strept. faecalis	—	2	0	0	0	0	1
			M	29	Candida	GI infection	0	0	0	0	0	0
Hatcher[32]	311	2 (0.6)	M	24	Candida	—	—	—	—	—	—	0
Present study	4	4 (—)	A	†	Mycobacterium chelonei† gram-neg. rod	—	0	0	0	0	0	0
			A	—	—	—	1	0	0	0	0	0
			M	2.5	Staph. aureus	Opiate addict	1	0	1	0	0	0
			M	‡	Spore-forming rod-like bacillus	—	1	0	0	0	0	0

TABLE III (continued)

Reports of Infection of Implanted Porcine Valve Heterografts

Author (Reference)	no. of PVH in Study	no. (%) of Inf. PVH (incidence)	Site of Inf. PVH	Time Bet. Impl. and Infection (mo)	Infecting Organism	Predisposing Factor	Total Patients With: PVH Sten.	PVH Reg.	Ring Abcess	PVH Leaf. Perf.	Perivalve Leak	Death Related to Infection
Totals		47	A = 16 (34%) M = 17 (36%) T = 1 (2%) P = 1(2%) A-V = 6 (13%) (—) = 6 (13%)				6 (13%)	7 (15%)	3 (6%)	0 (—)	1 (2%)	19 (40%)

* Infection suspected but not proved.
† Grown from aortic tag in culture taken at time of operation; valve itself not cultured.
— = data not available.
‡ Duration of infection could not be determined.
α-Strept. = alpha-hemolytic Streptococcus; A = aortic; A-V = atrioventricular (site not specified); Bet. = between; GI = gastrointestinal tract; GU = genitourinary tract; H = Hemophilus; Impl. = implantation; Inf. = infected; Leaf. = leaflet; M = mitral; neg. = negative; P = pulmonary; Perf. = perforation; PVH = porcine valve heterograft; Reg. = regurgitation; S = sterile; Staph. = Staphylococcus; Sten. = stenosis; T = tricuspid.

of the valve, even though bacterial colonies and necrotic leaflet tissue and vegetations were found when the heterograft was removed. The patient had not received antibiotic therapy before operation. Because the heterograft had been in place for 2 1/2 years, it seems likely that the infection was acquired after implantation rather than at the time of operation. Although it is possible that the infection was related to the cardiac catheterization performed before removal of the infected heterograft, the catheterization was undertaken because the patient already had evidence of obstruction to flow through the heterograft. Thus, ultrastructural study provided the only unequivocal evidence that the porcine valve heterograft in this patient was infected.

The histologic and ultrastructural findings on the porcine valve heterograft from Patients 2 and 3 show that severe destruction of the collagen framework can occur in infection of valve bioprostheses. In Patient 3, invasion and colonization by Staphylococcus aureus was observed not only within the vegetations filling the cusps of the heterograft but also deep in the leaflets. The severe destruction and necrosis of the collagen bundles in sites of deep penetration and colonization of the organisms can be attributed to proteolytic enzymes released by inflammatory cells and bacteria. Polymorphonuclear leukocytes and macrophages are known to produce a specific collagenase,[45,46] but Staphylococcus aureus is not. Nevertheless, the destructive effects of staphylococcal infections on native cardiac valves are well known. In the valve of Patient 2, inflammatory cells were localized only in the vegetations on the surface of the valve and not within the leaflets. This absence of inflammatory cells from deep areas of infected porcine valve heterografts is in keeping with previous observations[35] showing that inflammatory cells in noninfected porcine heterografts show no tendency to invade the leaflets but tend to remain localized on the surfaces.

Many of the staphylococci in the valve from Patient 3 had undergone morphologic changes, including increase in cell size and thinning of the cell walls, which probably resulted from treatment of the patient with nafcillin for 6 weeks before valve replacement. Such ultrastructural features have been described in penicillin-treated staphylococci.[38,47] However, not all of the bacteria were in a stage of lysis or degeneration. The colonies of bacteria situated in the collagen of the leaflet showed only slight morphologic changes, and a few of these bacteria appeared to be in the process of cell division. This would indicate that the antibiotic therapy was not effective against the deeper-penetrating bacteria and that some of the bacteria were still viable at the time of valve removal. This observation is consistent with the detection of Staphylococcus aureus on culture of the porcine valve heterograft at the time of removal.

Review of clinical and pathologic changes reported in infection of porcine valve heterografts: Including the 4 valves in the 4 patients in our study, infection in porcine valve heterografts has been reported in a total of 47 valves implanted in 47 patients.[18–32]

Because of the limited amount of information presented in many of these reports, the following data almost certainly underestimate the true incidence of the findings. Nevertheless, some useful generalizations can be derived from review of the observations in these patients (Table III). Two porcine valve heterografts had been implanted in at least 4 of the 47 patients; however, none of these 4 patients had infection in more than one heterograft, and the most downstream valve was the one always infected. Seventeen of the infected heterografts were in the mitral position, 16 in the aortic position, 1 in the tricuspid position and 1 in the pulmonary position; the site of implantation of the remaining 12 valves was not reported. In 6 patients, the infection occurred within 2 months after implantation; in 23 other patients, it became evident more than 2 months after implantation (maximal time 45 months), and in 18 patients the time at which infection developed was not specified.

Bacteriologic identification of a total of 24 infecting organisms was reported in 22 valves: Eleven of these organisms were streptococci, 3 staphylococci; 4 gram-negative rods and 4 fungi (including 3 candida species and 1 phycomyces). In two other valves (from two of our four patients) organisms were seen on morphologic study but were not identified bacteriologically.

The single factor most frequently identified as predisposing to infection of porcine valve heterografts was opiate addiction (five patients). All five patients had undergone implantation of a porcine valve heterograft as part of therapy for a separate episode of infective endocarditis involving the patient's own valve.

Dysfunction was reported to occur in 14 of the infected heterografts: 6 heterografts had stenosis due to vegetations interfering with cuspal motion; 7 had regurgitation, although perforation of the cusps was not specifically reported in any valve, and one had a perivalve leak. Valve ring abscesses were described in three patients, but were sterile in two of them. Of the 47 patients, 19 (40 percent) died of various complications of infection (Table III).

Comparison of features of infection involving porcine valve heterografts and other types of prosthetic heart valves: These observations show that infection of porcine valve heterografts differs in several respects from infection involving other types of prosthetic heart valves. There are several characteristics of infection of rigid-framed prosthetic valves[1–18]: (1) The infection does not involve the prosthetic material; instead, it involves biologic materials such as fibrin, organized thrombi and fibrous tissue that have covered the prosthetic valve; (2) the infection is characteristically located at the site of attachment of the sewing ring to host tissue; (3) valve ring abscesses are to be expected; and (4) the infection does not destroy the prosthesis itself although it may cause it to malfunction mechanically and to become detached from the valve ring.

In contrast to these characteristics of infection of rigid-framed prosthetic valves, infection of porcine valve heterografts has the following features: (1) It can involve the prosthetic material itself as well as fibrin, organized thrombi and fibrous tissue from the host; (2) it is localized in the cusps; (3) it can destroy the prosthesis itself and (4) it is uncommonly associated with valve ring abscesses. The destruction of bioprosthetic tissue is illustrated by our observations of invasion of the leaflet substance and severe breakdown of collagen in the heterografts from two or our patients (Patients 3 and 4). This pattern of localization of infection of porcine valve heterografts is similar to that reported in other types of bioprostheses, including homografts,[48–54] fascia lata valves[55–57] and pericardial valves.[57]

Perforation occurring in a cusp of a porcine valve as the result of infection has not been reported, in spite of the potential for destruction of infected bioprosthetic tissue, although prosthetic regurgitation due to unspecified anatomic lesions has been found in infected porcine valves (Table III). Perforations of the leaflets of porcine valves appear to be consequences of degenerative breakdown of their connective tissue.[35] Thus, the observations just reviewed suggest that, probably because of the glutaraldehyde treatment, porcine valve heterografts are less easily destroyed by infections than are native valves, homografts and fascia lata valves.

Prosthetic valve stenosis caused by infected vegetations appears to be a relatively common complication of porcine heterograft infection (Table III). This complication must be distinguished from obstruction to flow caused either by calcific deposits in the leaflets, with resulting loss of mobility, or by the presence of large noninfected thrombi within the cusps.

Valve ring abscesses and perivalve leaks (occurring in 3 and 1, respectively, of 47 patients) appear to be uncommon (Table III) when porcine valves become infected. The incidence rate of valve ring abscesses in patients with rigid-framed prosthetic valves is high. Arnett and Roberts and their co-workers[14,18] found valve ring abscesses in each of their 22 patients with fatal infection of rigid-framed prosthetic valves, and the entire circumference of the valve anulus was necrotic in two thirds of these patients.

The mortality rate of infection of porcine valve heterografts is high (40 percent) in spite of what appear to be more favorable characteristics of infection (Table III). Nevertheless, the data available are incomplete, and the number of patients whose exact cause of death was reported is too small for a meaningful analysis.

Possible mechanisms of infection of prosthetic heart valves: Although the site of infection might be expected to be similar in rigid-framed prostheses and in porcine valve heterografts, because the devices have similar sewing rings, this is not the case. In our Patient 1, fibrin deposits were the sites of localization of small bacterial colonies considered to represent early stages of infection. This observation is in accord with the results of ultrastructural studies of the early stages of infection in experimentally induced infective endocarditis in animals.[58–61] Those studies have shown that fibrin-platelet microthrombi are the sites of initial attachment and colonization of valves by bacteria and that denudation of valve endothelium (which exposes the highly thrombogenic connective tissue of the sub-

endothelial region) is the factor leading to the formation of these microthrombi. It is known[35,62,63] that nonimplanted glutaraldehyde-stabilized porcine valve heterografts are denuded of endothelium and that after implantation they become covered with a layer of fibrin. This layer of fibrin, which does not become covered by endothelium or a fibrous sheath, appears to be the preferred site of bacterial invasion. It has been suggested that the sites of infection in rigid-framed prosthetic heart valves are small platelet-fibrin thrombi that become organized by undergoing fibroblastic invasion and grow to cover portions of the sewing cloth of the prosthesis.[64] A similar process of growth of host fibrous tissue occurs in implanted porcine valve heterografts. However, for reasons that may be related to the glutaraldehyde treatment of the porcine tissue, the ingrowth of host fibrous tissue does not extend into the cusps themselves.[35,62,63] Thus, bacteria appear to be more likely to colonize the fibrin on the cusps than the organizing fibrous tissue in the sewing ring.

In conclusion, our study shows that bacterial infections of porcine valve heterografts involve the valve cusps and can cause considerable destruction of prosthetic tissue. Such infections probably begin with the attachment of bacteria to the fibrin deposits that form on the cusp surfaces. Review of previous reports indicates that these infections have a high mortality rate, although they are not frequently associated with valve ring abscesses. Ultrastructural study can be of considerable value in assessing the extent of prosthetic tissue damage and in determining the nature of the bacterial infection.

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Cardiac Pacing

1 SAFETY

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3



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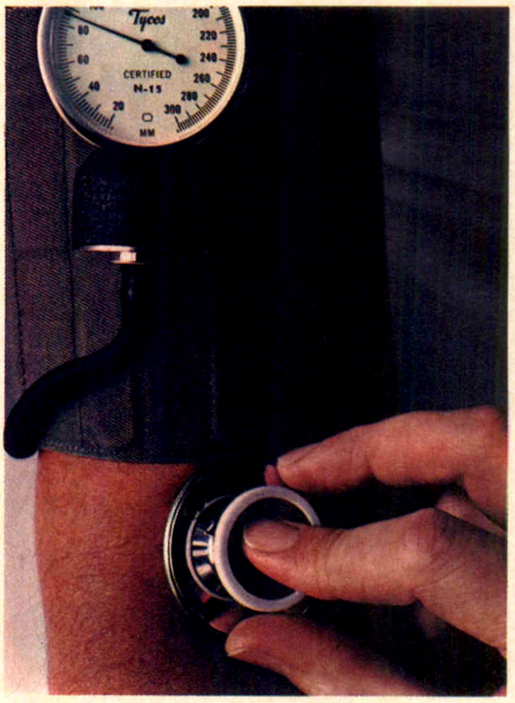
because INDERAL, alone or in combination with other agents, has established a remarkable record of blood pressure control. Another encouraging sign: increased dosage usually does not produce proportional decreases in heart rate.

Proper patient selection is important: INDERAL should be employed only in the absence of congestive heart failure, sinus bradycardia, or heart block greater than first degree.*

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Effective in b.i.d. dosage

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(PROPRANOLOL HCl)

B.I.D.

FOR HYPERTENSION

40 mg and 80 mg tablets

*Please see the following page for brief summary of prescribing information on warnings, including avoidance of abrupt withdrawal, contraindications, and adverse reactions.

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BRIEF SUMMARY
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propranolol hydrochloride
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BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

The mechanism of the antihypertensive effects of INDERAL has not been established. Among the factors that may be involved in the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

INDICATIONS

Hypertension
INDERAL is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. INDERAL is not indicated for treatment of hypertensive emergencies.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short term memory loss; emotional lability; slightly clouded sensorium; and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION

ORAL

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 40 mg INDERAL twice daily, whether used alone or added to a diuretic. Dosage may be increased gradually until adequate blood pressure is achieved. The usual dosage is 160 to 480 mg per day. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower doses are used, may experience a modest rise in blood pressure toward the end of the 12 hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or 3 times daily therapy may achieve better control.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg); IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED

INDERAL
(propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 462—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

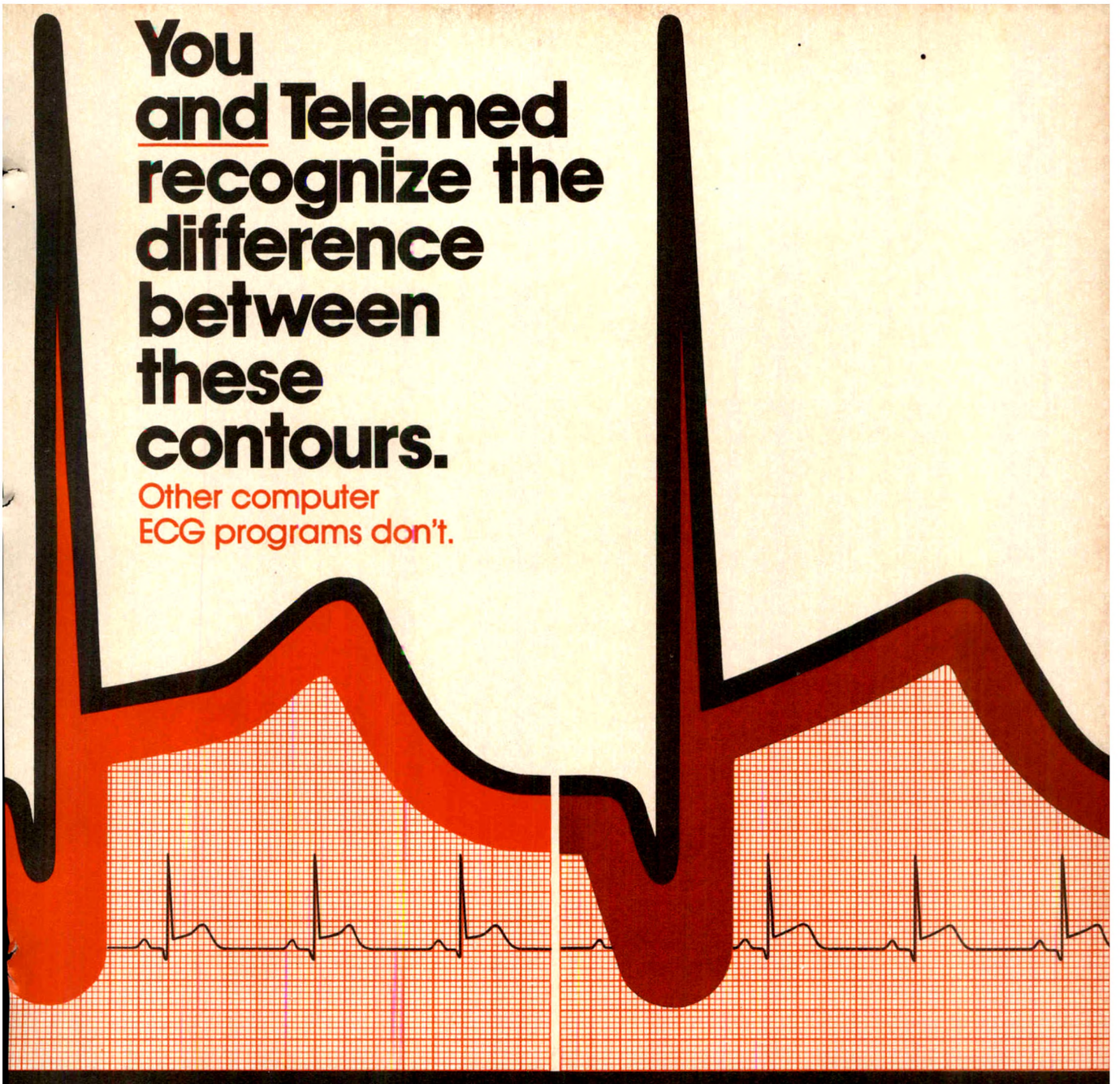
No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

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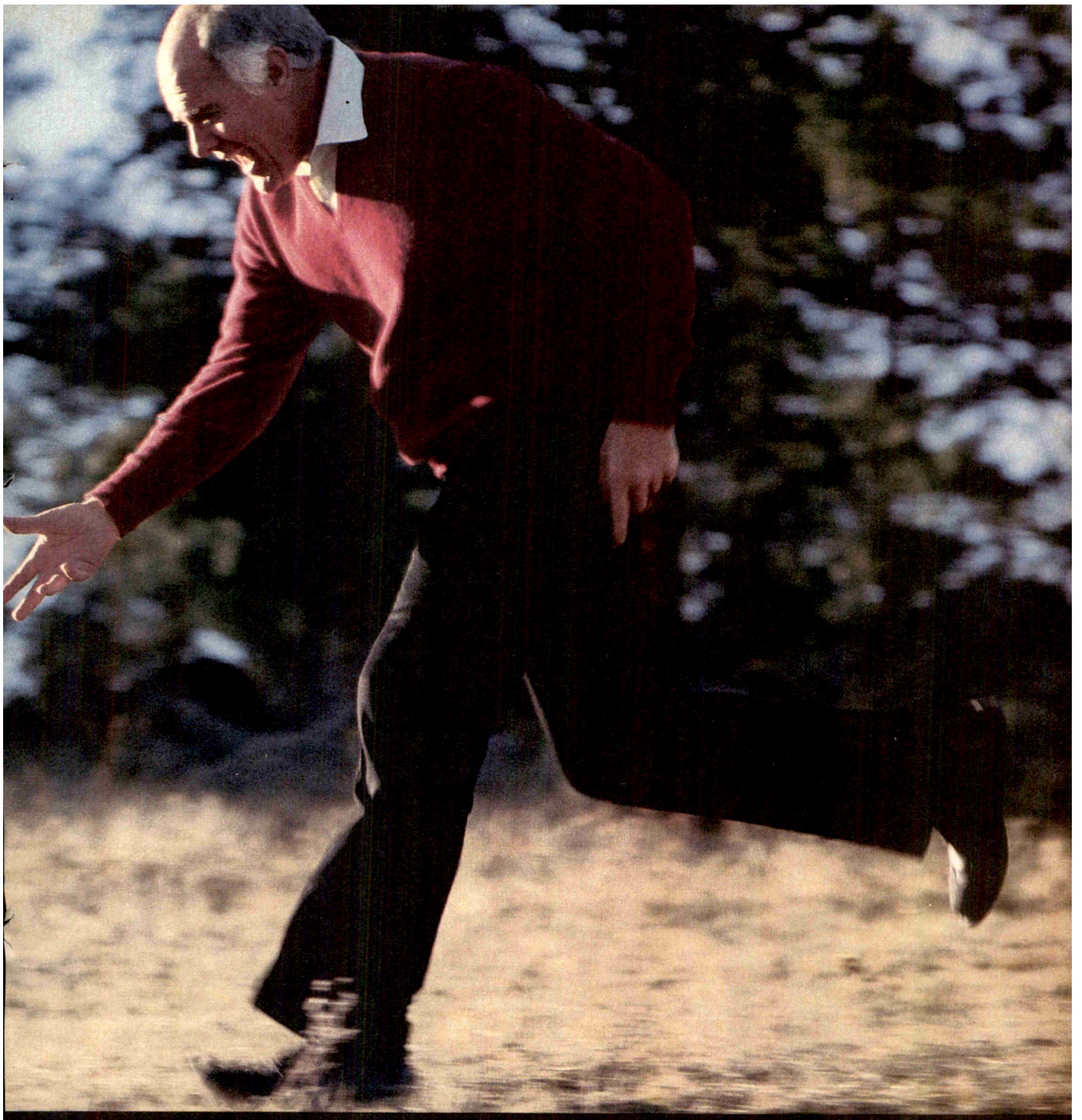
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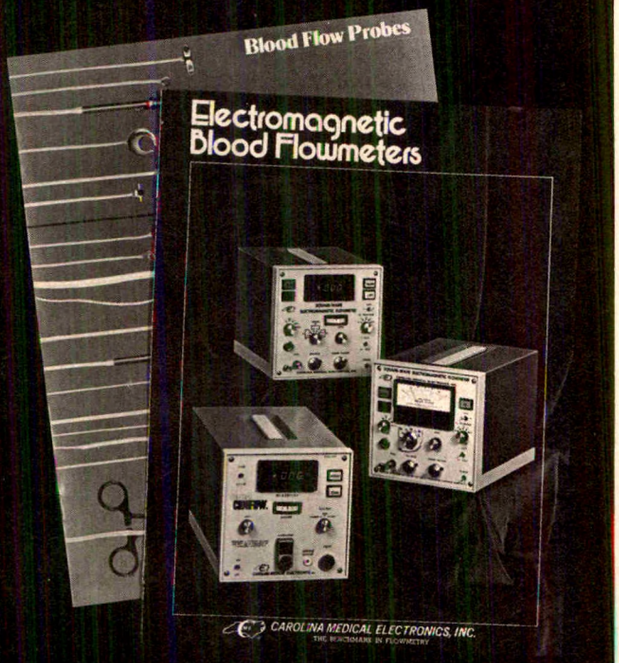
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ALDACTONE®

(spironolactone) 25 mg. tablets

WARNING

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

For hypokalemia: 25 to 100 mg. daily in divided doses.

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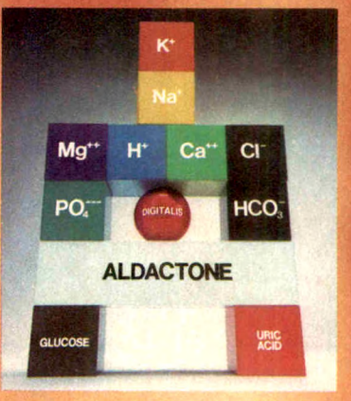
The delicate balance during treatment of CHF



Electrolyte imbalance is often a problem during digitalis therapy and most diuretics can worsen the problem. With both the thiazides and furosemide, fluid and electrolyte imbalance may lead to digitalis toxicity.

Aldactone for concomitant digitalis/diuretic therapy.
Aldactone® (spironolactone) provides gradual and sustained diuresis and, through a unique mechanism, helps prevent hypokalemia with limited risk of hyperkalemia. *Plus* . . . Aldactone does not adversely affect serum calcium, magnesium, and uric acid levels nor alter glucose tolerance.

Limitations to consider.
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Thus Aldactone should be prescribed only when other measures are considered inadequate or inappropriate. (See boxed warning and *Warnings* section of Aldactone prescribing information, a brief summary of which appears on the facing page.)



SEARLE

Aldactone®
(spironolactone) 25-mg. tablets

The diuretic that helps maintain the delicate balance of electrolytes . . . when other measures are considered inadequate or inappropriate.

Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the facing page.





For nine and a half years Quinaglute® (quinidine gluconate) has kept the pace for Mary L.*

*Based on actual case history (photos posed by professional model).

Time-proven Quinaglute® DURA-TABS® (quinidine gluconate) 324 mg keeps the pace for patients with cardiac arrhythmias

For Mary L. and hundreds of thousands of cardiac patients, QUINAGLUTE® Dura-Tabs® have helped maintain the pace of normal sinus rhythm over long-term therapy. In the 19 years since its introduction, QUINAGLUTE has amassed an impressive clinical record of therapeutic efficacy, safety and patient acceptance.

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Time-proven for safety

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- 19 years of patient and physician acceptance

Time-proven for patient compliance

- convenient dosage schedule that's easy to remember: 1 to 2 Dura-Tabs® every 8 or 12 hours
- h.s. dose helps avoid early morning reversion

Contraindications: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects, ventricular premature beats, ventricular tachycardia or flutter while on the drug.

Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances. 101-71

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For full information please refer to package insert.

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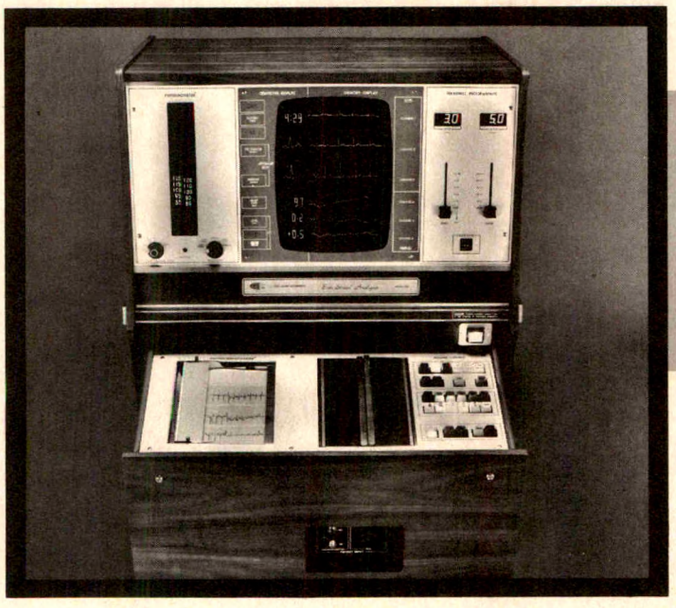
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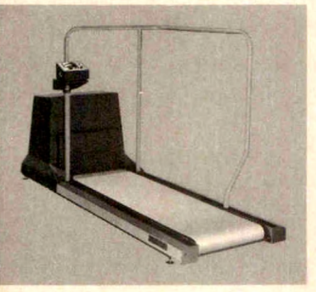
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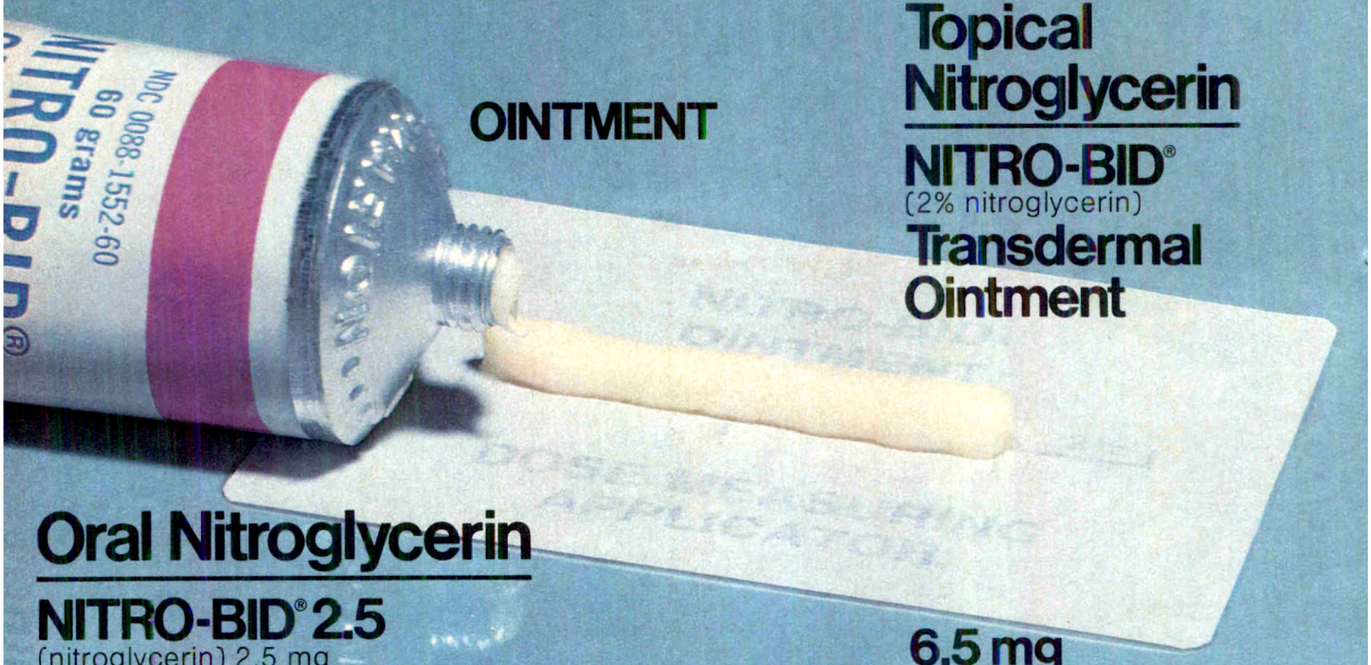
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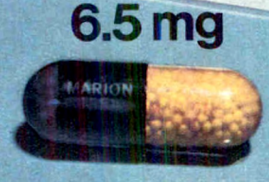
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Indications
Based on a review of this drug and a related drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective. When taken by the oral route, NITRO-BID Capsules are indicated for the management, prophylaxis or treatment of anginal attacks.

"Possibly" effective. When applied topically, NITRO-BID Ointment is indicated for the prevention and treatment of angina pectoris attacks especially at night.

Final classification of the less-than-effective indications requires further evaluation.

Contraindications
Patients with marked anemia, increased intraocular pressure, increased intracranial pressure, glaucoma, hypotension, and idiosyncrasy to this drug.

Warnings
NITRO-BID is not intended to abort the acute anginal episode. NITRO-BID Capsules must be taken ORALLY, not sublingually. In terminating NITRO-BID Ointment treatment, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions.

Precautions
A headache is a definite sign of overdosage and, therefore, dosage should be reduced. Occasionally, elderly patients may have no untoward symptoms while recumbent, but may develop postural hypotension with faintness upon suddenly arising.

Adverse Reactions
With use of nitrates, transient headache, postural hypotension, flushing, tachycardia and dizziness may occur.

Consult full product disclosure before prescribing.

WITHOUT COMPROMISE OF VITAL ORGANS



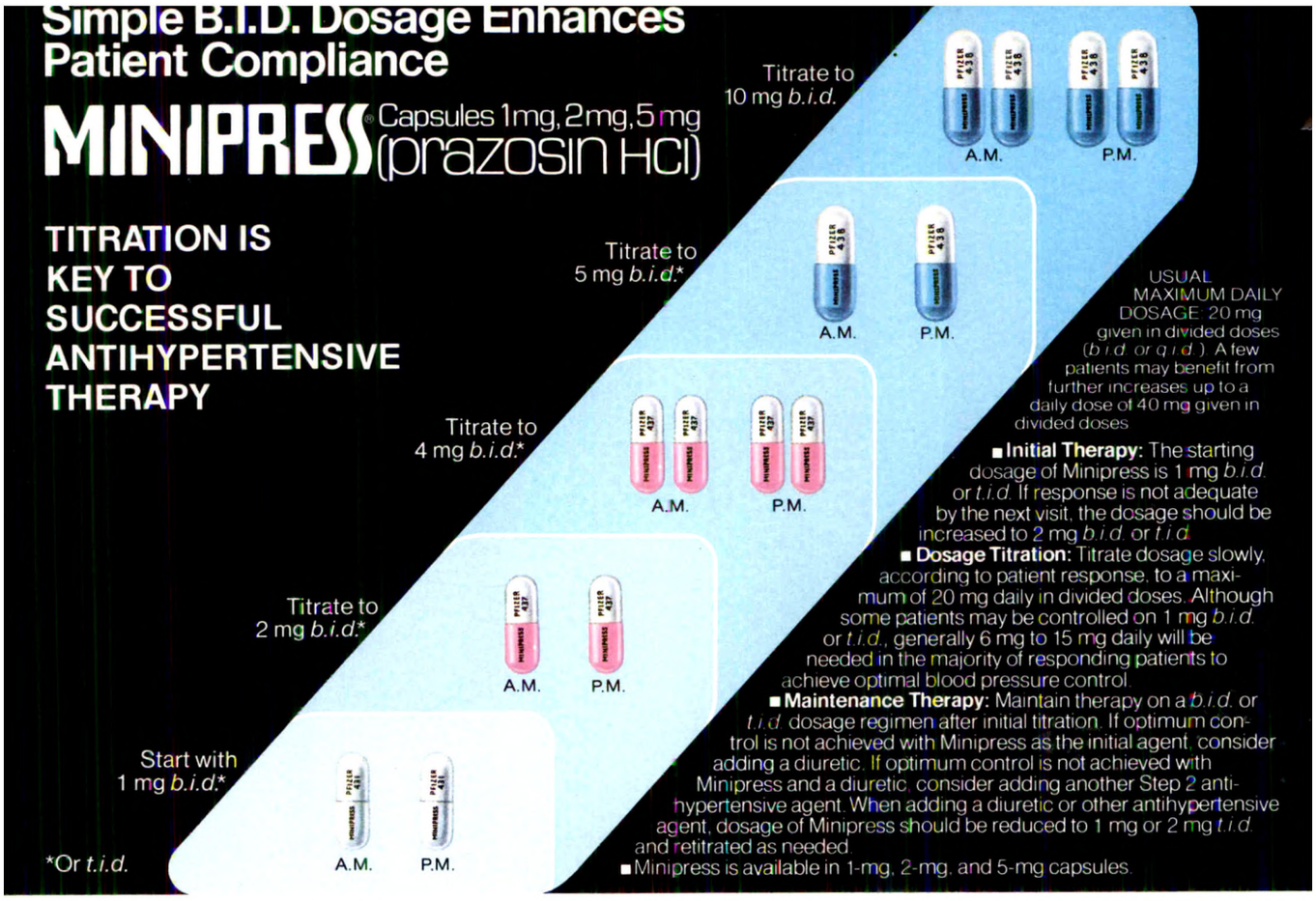
Please see Brief Summary on last page
Before prescribing Minipress, WARNINGS and DOSAGE AND ADMINISTRATION sections should be carefully reviewed.

MINIPRESS® Capsules 1mg, 2mg, 5mg
(prazosin HCl)

Simple B.I.D. Dosage Enhances Patient Compliance

MINIPRESS® Capsules 1mg, 2mg, 5mg (prazosin HCl)

TITRATION IS KEY TO SUCCESSFUL ANTIHYPERTENSIVE THERAPY



*Or t.i.d.

USUAL MAXIMUM DAILY DOSAGE: 20 mg given in divided doses (b.i.d. or q.i.d.). A few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses.

■ **Initial Therapy:** The starting dosage of Minipress is 1 mg b.i.d. or t.i.d. If response is not adequate by the next visit, the dosage should be increased to 2 mg b.i.d. or t.i.d.

■ **Dosage Titration:** Titrate dosage slowly, according to patient response, to a maximum of 20 mg daily in divided doses. Although some patients may be controlled on 1 mg b.i.d. or t.i.d., generally 6 mg to 15 mg daily will be needed in the majority of responding patients to achieve optimal blood pressure control.

■ **Maintenance Therapy:** Maintain therapy on a b.i.d. or t.i.d. dosage regimen after initial titration. If optimum control is not achieved with Minipress as the initial agent, consider adding a diuretic. If optimum control is not achieved with Minipress and a diuretic, consider adding another Step 2 antihypertensive agent. When adding a diuretic or other antihypertensive agent, dosage of Minipress should be reduced to 1 mg or 2 mg t.i.d. and retitrated as needed.

■ Minipress is available in 1-mg, 2-mg, and 5-mg capsules.

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Pfizer **LABORATORIES DIVISION**
PFIZER INC.

Effect of Diltiazem, a Calcium Antagonist, on Myocardial Ischemia

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In line with studies on the metabolism of the ischemic myocardium, the effectiveness of diltiazem hydrochloride, a potent calcium antagonist, in reducing the effects of ischemia was evaluated. Nonischemic and ischemic tissue samples were examined in two groups of dogs—Group I, dogs receiving no drug and killed after 60 minutes of regional ischemia, and Group II, dogs given diltiazem after 10 minutes of ischemia and killed 50 minutes later. Administration of diltiazem proved beneficial in several ways: The decrease in adenosine-5′-triphosphate in the ischemic region was halved, inhibition of anaerobic glycolysis was reduced, tissue levels of lactic acid and free fatty acids were lowered and the contractility of glycerinated heart muscle fibers was improved. However, administration of the drug did not influence mitochondrial function. Mitochondrial oxygen consumption and respiratory control were reduced by equal amounts in both groups, as was mitochondrial calcium ion binding. These observations demonstrate that diltiazem is capable of minimizing the consequences of acute ischemia, although the beneficial effects do not extend to all aspects of myocardial metabolism.

Diltiazem hydrochloride is a potent calcium antagonist as well as a coronary vasodilator.[1–3] The presence of even minute amounts of the compound causes relaxation of smooth muscle in coronary arteries; this effect can be reversed by increasing calcium concentration.[4] Diltiazem also diminishes contractility of left atrial preparations[5] and reduces cardiac output, venous return and heart rate when administered to patients.[6,7] Saikawa et al.[8] described the drug as an inhibitor of the transmembrane "slow channel" through which calcium ions enter the cell. This action differs from that of many other antianginal drugs, such as nitroglycerin, which appear to act primarily by redistribution of systemic and coronary blood flow.[9,10]

Various pharmaceutical preparations have been cited in recent years as reducing the acute effects of ischemia on the myocardium. The modes of action of these agents include stimulating anaerobic glycolysis,[11] enhancing substrate transport[12] and reducing myocardial oxygen demands.[13] In many cases the support for such effects is based on data from noninvasive techniques such as measurements of creatine kinase release or S-T segment changes.[14] In this investigation we assessed the effect of diltiazem on the ischemic myocardium by analysis of metabolic function within the occluded tissue, and the results compared with findings in ischemic tissue taken from dogs receiving no drug.

Methods

Experimental procedure: Experiments were conducted in healthy mongrel dogs of similar age and size. After anesthesia with sodium pentobarbital (30 mg/kg body weight), respiration was maintained through an endotracheal tube attached to an intermittent positive pressure respirator (Air Shield, Inc., Hatboro, Pennsylvania). A left thoractomy was performed between the fourth and fifth ribs, and the pericardium incised and sutured to the chest wall.

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Ischemia was initiated by ligating several (three to five) smaller branches of the left anterior descending coronary artery with 2-0 silk sutures. This procedure severely reduced flow to the area and resulted in an ischemic region of about 2.5 to 3 cm in diameter. Assessment of epicardial S-T segment elevations and the degree of visible cyanosis was used to delineate the ischemic region. In several dogs 2.5 to 5 ml of 10 percent alphazurine 2G blue dye was injected in the manner described by Kane et al.[15] 5 minutes before the animals were killed. This dye stains only well perfused tissue and permitted further demarcation of the ischemic region.

Two groups of dogs were examined: In Group I, no medication was given during the ischemic period, and in Group II, diltiazem hydrochloride was administered as a bolus injection (0.2 mg/kg, dissolved in sterile saline solution) 10 minutes after coronary arterial ligation. This time of injection was chosen because under clinical conditions it is not possible to predict the onset of acute myocardial ischemia. Animals in both groups were killed after 60 minutes of ischemia.

Tissue samples: Immediately before the animals were killed two tissue samples (500 mg) were taken from both the ischemic and nonischemic regions using tissue tongs precooled for several minutes in liquid nitrogen. These samples contained predominantly subepicardial tissue. The ischemic samples were taken from the center of the infarct and nonischemic samples from an area 3 to 4 cm from the edge of visible cyanosis. One sample from each region was used to determine the level of several glycolytic intermediates and the other for estimating the concentration of several high energy phosphates. All samples were wrapped in aluminum foil and stored in liquid nitrogen until they could be analyzed. The heart was then removed quickly and washed successively in two beakers containing ice-cold saline solution. The left ventricle was then divided into ischemic and nonischemic portions. Samples weighing approximately 2 g were taken from both regions and placed in a glycerol solution for eventual analysis of in vitro contractility. Small pieces of tissue (500 mg) were taken for determining the levels of free fatty acids. These were stored at the temperature of liquid nitrogen until analysis. Finally, the remaining tissue (7 to 10 g) was used for the immediate isolation of mitochondria.

Glycolytic pathway intermediates, high energy phosphates and free fatty acids: The following glycolytic intermediates were measured in perchloric acid extracts of the frozen sample: lactate, pyruvate, alpha glycerophosphate (α-GP), dihydroxyacetone phosphate (DHAP), glucose-6-phosphate (G-6-P), fructose-6-phosphate ((F-6-P) and fructose-1,6-diphosphate (F-1,6-DP). The myocardial redox state was monitored by comparing the ratio of lactate to pyruvate and of α-GP to DHAP. In addition, glycolytic flux through phosphofructokinase, a key regulatory enzyme for anaerobic glycolysis, was estimated using the following formula:

$$\text{Glycolytic flux} = ([\text{G-6-P}] + [\text{F-6-P}])/[\text{F-1,6-DP}].$$

Tissue levels of the following high energy phosphate were measured: creatine phosphate (CP), adenosine-5′-triphosphate (ATP) and adenosine-5′-diphosphates were determined using standard procedures which use NADH-coupled reactions.[16]

Tissue levels of the following free fatty acids were measured: myristic ($C_{14:0}$), palmitic ($C_{16:0}$), stearic ($C_{18:0}$), oleic ($C_{18:1}$) and linoleic ($C_{18:2}$). The analysis was performed according to procedures outlined by Ramadoss et al.,[17] with slight modifications. Fatty acids were extracted from the tissue samples with peroxide-free ether, reduced to their methyl esters and separated using a Packard gas chromatograph (model 7400, Packard Instrument Company, Downers Grove, Illinois). A 6 foot glass column (2 mm in diameter) was packed with 10 percent SP-22-PS (Supelco, Inc., Bellefonte, Pennsylvania). Nitrogen was used as the carrier gas.

Contractility of glycerinated muscle fibers: The apparatus and procedures used to study in vitro contractility have already been extensively described elsewhere[18,19] and will be discussed here only briefly. Essentially the procedure of Julian[20] was employed. Tissue samples were first immersed in a glycerol solution containing 50 percent glycerol, 20 millimolar (mM) imidazole, 4 mM EGTA (neutralized ethyleneglycol-bis-(beta-aminoethyl ether) N,N′-tetraacetic acid) and 1 mM dithiothreitol, pH 7.0. They were stored in this solution for 24 hours at 0° C. The samples were then transferred to fresh medium and stored at −24° C for 1 week.

One hour before analysis the samples were removed from the glycerol solution and immersed in a relaxation solution containing the following: 100 mM potassium chloride, 5 mM magnesium chloride, 5 mM Na_2ATP, 5 mM EDTA, 5 mM NaN_3, and 20 mM imidazole, pH 7.0, at 0° C for 1 hour. Fiber bundles roughly 2.5 mm in length with a 0.15 mm^2 cross-sectional area were then dissected from each sample. A single fiber bundle was secured between a servo system and a force transducer by two stainless steel wires. Once secured, the relaxation solution was quickly removed and replaced by a contraction solution containing the following: 100 mM KCl, 5 mM $MgCl_2$, 5 mM Na_2ATP, 5 mM EGTA, 5 mM NaN_3, 20 mM imidazole, and 5 mM $CaCl_2$, pH 7.0. Under this condition the servo system maintained constant length while increasing tension was recorded. From the data obtained during this isometric contraction, the following indexes were determined: maximal developed tension (P_0), time to peak tension (t_0) and the maximal rate of tension development (dP/dt_{max}). One to two preparations were obtained from each glycerinated muscle.

Mitochondrial studies: Mitochrondria were isolated according to the procedures described by Sordahl et al.[21] with some modifications. Tissue samples were placed in an ice-cold homogenization solution composed of 0.18 molar (M) potassium chloride, 0.01 M Na_2EDTA and 0.01 M Tris, pH 7.4. The tissue was first finely minced using scissors rinsed in the homogenization solution and then homogenized using a Brinkman Polytron (model PT-20, Brinkman Instruments, Inc., Westbury, New York). The homogenate was centrifuged at 500 × *g* for 10 minutes, and the supernatant obtained was centrifuged at 12,000 × *g* for 15 minutes. The pellet obtained was resuspended in the homogenization solution and centrifuged at 12,000 × *g* for 10 minutes. This step was repeated once, and the final mitochondrial pellet was suspended in either the homogenization solution (for respiration studies) or in 0.18 M KCl and 0.01 M Tris, pH 7.4 (for calcium-binding studies).

Mitochondrial respiration was measured using a Gilson Oxygraph equipped with a vibrating plantinum electrode[21] (Gilson Medical Electronics, Inc., Middleton, Wisconsin). The reaction medium contained the following: 0.25 M sucrose, 8.5 mM $K_2HPO_4 \cdot 3H_2O$, 0.01 M Na_2EDTA and 0.01 M Tris, pH 7.4. Substrates used were glutamate (7.5 mM) plus oxaloacetate (1.5 mM), succinate (7.5 mM) with rotenone (5 μg/mg protein) added to inhibit NAD-linked respiration, or ascorbate (5 mM) plus N,N,N′,N′-tetramethyl-p-phenylenediamine (TMPD) (0.2 mM). Active respiration was initiated by the addition of 600 ± 30 nmoles of ADP. The assay temperature was maintained at 30° C, and the total volume was 1.8 ± 0.1 ml.

Mitochondrial calcium binding was determined at 37° C according to the millipore filter method of Harigaya and Schwartz[22] with some modifications. The medium used to

measure binding consisted of 20 mM Tris-maleate (pH 6.8), 50 mM KCl, 10 mM $MgCl_2$, 50 $\mu m^{45}CaCl_2$ (0.166 μCi/ml), 0.25 mM Na_2ATP and 0.40 mg/ml mitochondrial protein. The reaction was started by the addition of protein and terminated by filtration through a Millipore filter (HAWP 01300 HA, 0.45 μ) using a Swinney adaptor (Millipore Corp., Bedford, Massachusetts). Calcium-45 activity in the ultrafiltrate was determined using a Packard liquid scintillation counter (model 3320, Packard Instrument Company, Downers Grove, Illinois) in a scintillator containing 2 percent ethyleneglycolmonoethylether, 10 percent naphthalene and 0.4 percent PPO, in dioxane. The calcium binding was estimated by subtracting the specific activity in the filtrate from that in the reaction mixture.

Material: Diltiazem hydrochloride (Herbesser®) was kindly provided by Tanabe Seiyaku Co., Osaka, Japan. Calcium-45 chloride was obtained from ICN Company, Irvine, California. Alphazurine 2G blue dye was obtained from Sigma Chemical Company, St. Louis, Missouri.

Statistical evaluation: Data were evaluated using the Student's t test. In each instance two statistical comparisons were made. Within each group, values obtained from the nonischemic region were compared with those of the ischemic zone. Also, ischemic values obtained from the dogs in Group I were compared with ischemic values from dogs in Group II. This distinction is indicated in Tables I to VII.

Results

The changes observed between nonischemic and ischemic regions were of sufficient magnitude to provide an effective basis for monitoring the consequences of diltiazem administration. Comparisons between ischemic regions in the control and diltiazem-treated animals were also made. Such comparisons were made on different animals and thus do not take into account individual differences between the animals used in each group. On the other hand, comparison of nonischemic and ischemic tissue from the same heart avoids this risk.

TABLE I

Levels of Several High Energy Phosphates in Nonischemic (NI) and Ischemic (I) Regions of the Heart*

Group	CP	ATP	ADP
Control group			
NI(7)	7.64 ± 0.66	3.97 ± 0.16	0.78 ± 0.07
I(7)	3.82 ± 0.53	2.11 ± 0.41	0.49 ± 0.07
± % (I vs. NI)	−50‡	−47‡	−37‡
Diltiazem group			
NI(4)	7.80 ± 1.13	3.98 ± 0.50	0.46 ± 0.07
I(4)	4.07 ± 0.58	3.03 ± 0.22	0.66 ± 0.10
± (I vs. NI)	−48‡	−24‡	+30†
Both groups			
± % (I, diltiazem vs. I, control)	+6	+36*	+26

† $0.05 < P < 0.10$.
‡ $P < 0.05$.
* Diltiazem (0.2 mg/kg) was administered intravenously 10 minutes after the onset of regional ischemia, and the dogs were killed 50 minutes later. Control animals were killed after 60 minutes of regional ischemia. Data represent the mean ± standard error of the number of samples in parentheses.
ATP = adenosine-5′-triphosphate; and ADP = adenosine-5′-diphosphate; CP = creatine phosphate. Units are μmoles/g wet weight.

High energy phosphates: Changes in nonischemic and ischemic levels of several high energy phosphates are depicted in Table I. ATP levels were reduced by roughly 50 percent of nonischemic values in the control (no drug) group, but this reduction was only 24 percent in the diltiazem-treated dogs. This represents a marked preservation of the energy reservoir in these animals. In addition, the decrease in ADP in the ischemic region was prevented by the administration of diltiazem (Table I). However, diltiazem did not prevent the ischemia-induced decrease in creatine phosphate. Statistical comparisons between ischemic regions in both groups revealed that ischemic levels of ATP were 36 percent higher in the diltiazem-treated animals than in the control dogs (Table I). This increase was of borderline significance ($0.05 < P < 0.10$). Creatine phosphate and ADP levels were also higher in the ischemic region of Group II dogs than in the corresponding region in Group I dogs.

Lactate levels and the myocardial redox state: The level of lactate in the ischemic region was considerably lower in the diltiazem-treated dogs than in the control animals (Table II). This difference, although large, was not statistically significant. Such a reduction combined with the diminished breakdown of ATP could be expected to limit the acidosis that normally accompanies ischemia. In addition to lactate, the level of alpha glycerophosphate in the occluded region in the diltiazem-treated dogs did not rise as high as that in ischemic tissue taken from control dogs (Table II).

TABLE II

Assessment of Myocardial Redox State in Nonisochemic (NI) and Ischemic (I) Regions of the Heart*

Group	Lactate	Pyruvate	L/P
Control group			
NI(5)	3,099 ± 772	153 ± 19	20.3
I(5)	14,190 ± 3,462	144 ± 10	98.5
± % (I vs. NI)	+356†	−6	+385
Diltiazem group			
NI(4)	2,172 ± 328	112 ± 20	18.5
I(4)	9,276 ± 2,421	117 ± 15	79.3
± % (I vs. NI)	+327†	+4	+329
Both groups			
± % (I, diltiazem vs. I, control)	−35	−19	−20

	α-GP	DHAP	α-GP/DHAP
Control group			
NI(5)	464 ± 144	70 ± 11	6.6
I(5)	1,693 ± 374	60 ± 22	28.2
± % (I vs. NI)	+265†	−17	+327
Diltiazem group			
NI(4)	294 ± 51	72 ± 19	4.1
I(4)	1,110 ± 107	57 ± 10	19.5
± % (I vs. NI)	+278	−26	+376
Both groups			
± % (I, diltiazem vs. I, control)	−34	−5	+15

* Diltiazem (0.2 mg/kg) was administered as indicated in Table I. Data represent the mean ± standard error of the number of samples in parentheses. α-GP = α-glycerophosphate; DHAP = dihydroxyacetone phosphate; L/P = lactate/pyruvate ratio. Units are nmols/g wet weight.
† $P < 0.05$.

Changes in the myocardial redox state were estimated by using as markers the ratios of lactate to pyruvate (L/P) and alpha glycerophosphate to dihydroxyacetone phosphate (α-GP/DHAP). Table II shows that ischemia produced a 3.9-fold increase in the L/P ratio in control animals and a 3.3-fold rise in the α-GP/DHAP ratio. Administration of diltiazem lessened to a slight degree the effect of ischemia on the L/P ratio, but had no effect on the rise in the α-GP/DHAP ratio in the occluded region (Table II).

Glycolytic flux (Table III): The level of both glucose-6-phosphate (G-6-P) and fructose-6-phosphate (F-6-P) increased sharply with ischemia in the control group. At the same time fructose-1,6-diphosphate (F-1, 6-DP) levels declined, indicating inhibition of phosphofructokinase (PFK). In dogs receiving diltiazem the elevations in G-6-P and F-6-P were about the same as in the dogs not receiving the drug, but the decrease in F-1, 6-DP was not as large (Table III). The degree of PFK inhibition in both groups was monitored by comparing the level of enzyme substrate to enzyme product: ([G-6-P] + [F-6-P])/[F-1, 6-DP]. This ratio was increased 2.8-fold in the control dogs, and only 1.6-fold in the diltiazem-treated animals, indicating that the inhibition of glycolytic flux at the PFK level was lessened by diltiazem administration. The differences between the level of these metabolites in the ischemic region of both groups was not significant.

Hemodynamics and in vitro contractility: Hemodynamic measurements were made at the following times: immediately before coronary arterial ligation, after 30 minutes of regional ischemia and after 60 minutes of ischemia. The measurements were made in four control and four diltiazem-treated dogs. The heart rate increased markedly in the control animals after ligation, rising from 137 beats/min before ligation to 157 beats/min after 30 minutes of ischemia. After 60 minutes of ischemia the heart rate fell slightly to 146 beats/min. The mean aortic pressure was similarly affected in these animals, increasing from 124 mm Hg before ligation to 168 mm Hg after 30 minutes of regional ischemia.

Diltiazem administration reversed these hemodynamic changes. The heart rate fell from a preligation level of 147 beats/min to 127 beats/min after 30 minutes of ischemia. After 60 minutes the heart rate was still low (125 beats/min). The mean aortic pressure was also reduced by diltiazem administration (99 mm Hg before ligation, falling to 85 mm Hg after 30 minutes and 84 mm Hg after 60 minutes of ischemia). Changes in left ventricular systolic and end-diastolic pressure, as well as the maximal and minimal rate of tension development (dP/dt_{max} and dP/dt_{min}, respectively) were similar in both groups.

Studies of in vitro contractility (Table IV) using glycerinated heart muscle fibers demonstrated that diltiazem administration led to a marked reduction in ischemia-induced damage to the contractile elements. In the animals not receiving diltiazem, values for maximal developed tension (P_0) and the maximal rate of tension development were reduced in ischemic muscle fibers by 52 and 61 percent respectively, of nonischemic levels. In addition, the time to peak tension (t_0) was prolonged by 90 percent in the ischemic fibers. These changes were much less pronounced in fibers prepared from ischemic tissue in the diltiazem-treated dogs. Table IV illustrates that P_0 was only 27 percent lower in ischemic than in nonischemic fibers, and dP/dt_{max} was only 31 percent reduced. In addition, values for t_0 were only 22 percent higher in ischemic than in nonischemic fibers in the animals treated with diltiazem.

Comparisons between ischemic fibers isolated from control and diltiazem treated groups revealed that values for P_0 were 49 percent higher in the dogs treated

TABLE III

Level of Hexose Phosphates in Nonischemic (NI) and Ischemic (I) Regions of the Heart*

Group	G-6-P	F-6-P	F-1,6-DP	([G-6-P] + [F-6-P])/[F-1,6-DP]
Control group				
NI(5)	265 ± 54	45 ± 10	160 ± 32	1.94
I(6)	417 ± 144	107 ± 32	72 ± 14	7.28
±% (I vs. NI)	+57	+138‡	−122‡	+275
Diltiazem group				
NI(6)	173 ± 22	43 ± 10	117 ± 10	1.85
I(5)	335 ± 87	100 ± 24	90 ± 10	4.83
±% (I vs. NI)	+94†	+133†	−30‡	+161
Both groups				
±% (I, diltiazem vs. I, control)	−20	−7	+25	−34

* Diltiazem (0.2 mg/kg) was administered as indicated in Table I. Data represent the mean ± standard error of the number of samples in parentheses. F-1,6-DP = fructose-1,6-diphosphate; F-6-P = fructose-6-phosphate; G-6-P = glucose-6-phosphate. Units are nmoles/g wet weight.
† $0.05 < P < 0.10$.
‡ $P < 0.05$.

TABLE IV

Contractility of Glycerinated Heart Muscle Fibers Isolated From Nonischemic (NI) and Ischemic (I) Regions of the Heart*

Group	P_0	t_0	dP/dt_{max}
Control group			
NI(5)	1785 ± 205	50 ± 8	7895 ± 1426
I(5)	855 ± 176	96 ± 25	3059 ± 1503
±% (I vs. NI)	−52‡	+92	−61‡
Diltiazem group			
NI(8)	1738 ± 94	47 ± 4	8623 ± 1143
I(6)	1271 ± 99	61 ± 14	5928 ± 1672
±% (I vs. NI)	−27‡	+30	−31
Both groups			
±% (I, diltiazem vs. I, control)	+49‡	−37	+48

* Diltiazem (0.2 mg/kg) was administered as indicated in Table I. Data represent the mean ± standard error of the number of preparations indicated in parentheses. dP/dt_{max} = maximal rate of isometric tension development (mg/min per mm^2); P_0 = maximal developed tension (mg/mm^2); t_0 = time to peak tension (seconds).
† $0.05 < P < 0.10$.
‡ $P < 0.05$.

with diltiazem (Table IV). This difference was of borderline significance ($0.05 < P < 0.10$). In addition, values for time to peak tension (t_0) were 37 percent lower in ischemic fibers from the diltiazem-treated animals than in fibers isolated from the same region in the control animals. The maximal rate of tension development (dP/dt_{max}) was also greater in these fibers than in ischemic fibers of Group I.

Mitochondrial respiration (Table V): Administration of diltiazem did not lessen the effect of ischemia on mitochondrial respiration. Reductions found in mitochondria isolated from ischemic tissue in the diltiazem-treated group were nearly identical with those found in the animals given no drug. Oxygen consumption was reduced by roughly 15 to 30 percent of nonischemic levels in both groups; the greatest reduction was found with the substrate that directs electrons into site I of the electron transport chain (glutamate-oxaloacetate). The respiratory control index was also reduced to a greater degree with this substrate. Site III (using ascorbate as substrate) was least affected by ischemia. No significant changes were found in the ADP/O ratios in either group. No significant difference in respiration was found between ischemic mitochondria isolated from the diltiazem-treated animals and those that received no drug.

Mitochondrial calcium binding (Table VI): Ischemia-induced reductions in mitochondrial calcium binding were also not improved by diltiazem administration. In fact, the reductions were somewhat greater in the diltiazem group than in the animals not given the drug. The ischemic mitochondria in both groups became quickly saturated with calcium ions at a level of 30 to 40 percent lower than that of the nonischemic mitochondria.

Tissue fatty acid (Table VII): Ischemia resulted in large increases in tissue levels of several free fatty acids within the occluded region. In the control group these elevations ranged from 54 percent above nonischemic levels for linoleic acid (18:2) to 174 percent for myristic acid (14:0). Fatty acid levels were similarly increased in the diltiazem-treated group. However, in this group the overall level of fatty acids was lower in both ischemic and nonischemic tissue. It is not certain whether this indicates that diltiazem has a direct effect on fatty acid metabolism. The levels of free fatty acids in ischemic tissue were lower in the diltiazem-treated dogs than in the control animals, but this difference was not significant.

TABLE V

Respiration of Mitochondria Isolated From Nonischemic (NI) and Ischemic (I) Regions of the Heart*

Group	R.C.I.	ADP:O	QO_2
Substrate: Glutamate-Oxaloacetate			
Control group			
NI(6)	9.4 ± 1.5	2.8 ± 0.1	133 ± 10
I(6)	5.9 ± 0.8	3.0 ± 0.1	94 ± 15
± % (I vs. NI)	−47†	+7	−29†
Diltiazem group			
NI(7)	7.4 ± 1.1	3.1 ± 0.1	131 ± 21
I(7)	5.2 ± 0.8	3.1 ± 0.1	94 ± 20
± % (I vs. NI)	−30	−	−29
Both groups			
± % (I-diltiazem vs. I-control)	−12	+3	−
Substrate: Succinate (Rotenone)			
Control group			
NI(6)	2.3 ± 0.2	1.6 ± 0.1	140 ± 9
I(6)	2.2 ± 0.2	1.4 ± 0.2	116 ± 19
± % (I vs. NI)	−4	−12	−17
Diltiazem group			
NI(7)	2.5 ± 0.2	1.6 ± 0.1	120 ± 16
I(7)	2.1 ± 0.2	1.6 ± 0.1	100 ± 12
± % (I vs. NI)	−16	−	−17†
Both groups			
± % (I, diltiazem vs. I, control)	−5	+14	−14
Substrate: Ascorbate-TMPD			
Control group			
NI(6)	1.3 ± 0.1	−	197 ± 10
I(6)	1.3 ± 0.1	−	170 ± 23
± % (I vs. NI)	−	−	−14
Diltiazem group			
NI(7)	1.4 ± 0.1	−	196 ± 23
I(7)	1.3 ± 0.1	−	163 ± 24
± % (I vs. NI)	−	−	−17
Both groups			
± % (I, diltiazem vs. I, control)	−	−	−4

* Diltiazem (0.2 mg/kg) was administered as indicated in Table I. Data represent the mean ± standard error of the number of samples indicated in parentheses. ADP:O = ratio of nmoles ADP phosphorylated to natoms of oxygen consumed; QO_2 = oxygen consumption in natoms oxygen consumed/min per mg mitochondrial protein; R.C.I. = respiratory control index.
† $P < 0.05$.

Discussion

In 1964 Fleckenstein[23] discovered that the action of certain drugs on the myocardium was similar to that observed during calcium deficiency. He found that these calcium-antagonistic compounds reduce myocardial adenosine triphosphate (ATP) consumption and inhibit excitation-contraction coupling.[24] As a consequence of

TABLE VI

Calcium Binding by Mitochondria Isolated From Nonischemic (NI) and Ischemic (I) Regions of the Heart*

Group	Binding Time 1 minute	2 minutes	3 minutes	4 minutes
Control group				
NI(5)	24 ± 5	33 ± 4	35 ± 2	37 ± 3
I(5)	21 ± 5	27 ± 3	27 ± 2	27 ± 3
± % (I vs. NI)	−13	−18	−23‡	−27‡
Diltiazem group				
NI(5)	27 ± 2	33 ± 4	34 ± 5	31 ± 6
I(5)	20 ± 2	25 ± 3	22 ± 3	19 ± 2
± % (I vs. NI)	−25‡	−24†	−35‡	−39‡
Both groups				
± % (I, diltiazem vs. I, control)	−5	−7	−19	−30

* Diltiazem (0.2 mg/kg) was administered as indicated in Table I. Data represent the mean ± standard error of the number of samples indicated in parentheses. Units are nmoles calcium bound/mg mitochondrial protein.
† $0.05 < P < 0.10$.
‡ $P < 0.05$.

TABLE VII

Free Fatty Acid Levels in Nonischemic (NI) and Ischemic (I) Regions of the Heart*

Group	Myristic	Palmitic	Stearic	Oleic	Linoleic
Control group					
NI(8)	16.3 ± 5.0	75.4 ± 20.5	72.6 ± 20.5	49.5 ± 6.1	32.2 ± 6.4
I(8)	44.7 ± 16.6	143.6 ± 46.2	140.8 ± 44.5	71.0 ± 15.8	49.7 ± 16.9
± % (I vs. NI)	+174†	+91†	+94†	+43	+54
Diltiazem group					
NI(5)	4.0 ± 1.6	44.4 ± 12.9	36.7 ± 8.1	27.2 ± 5.4	20.5 ± 4.3
I(5)	18.1 ± 7.9	82.7 ± 31.1	68.4 ± 22.9	44.3 ± 12.9	27.3 ± 7.4
± % (I vs. NI)	+353†	+86	+86	+63	+33
Both groups					
± % (I, diltiazem vs. I, control)	−146	−74	−106	−60	−82

* Diltiazem (0.2 mg/kg) was administered as indicated in Table I. Data represent the mean ± standard error of the number of samples in parentheses. Units are μg/g wet weight.
† $0.05 < P < 0.10$.

the decrease in high energy phosphate consumption, the calcium antagonists also reduce the cardiac oxygen requirement.[24]

Diltiazem belongs to a group of potent calcium antagonists that also includes verapamil and nifedipine.[4] In the present study the drug was administered 10 minutes after the onset of ischemia in order to simulate the clinical situation more closely than is usual. In preliminary studies we found that diltiazem is capable of protecting the mitochondria from the effects of reperfusion after a period of ischemia (unpublished observation). This may be due to the calcium-antagonistic properties of the drug because several authors[25,26] have implicated a rapid transmembrane influx of calcium as the major factor responsible for the structural damage that accompanies reperfusion.

Little information is available on the use of calcium-antagonistic compounds to reduce the effects of acute myocardial ischemia. Peng et al.[27] found that the mitochondrial defects normally observed in ischemic and ischemic-reperfused mitochondria are reversed when EDTA or EGTA are included in the isolation medium. Also, verapamil and prenylamine, as well as several other calcium-antagonistic compounds, have been shown to reduce the effects of angina pectoris.[24]

In the present experiments, we made statistical comparisons in two ways: (1) Within each group we compared values from the nonischemic and ischemic zones. (2) We compared values obtained from the ischemic regions in the control and diltiazem-treated dogs. Because this latter determination does not take into account individual differences among the animals used in each group, we used both methods to gain a more complete picture of the differences between the animals that did and did not receive diltiazem.

Mechanism of effect of diltiazem on myocardial ischemia: When administered after ligation of the coronary arteries, diltiazem lessened the effects of ischemia in several ways, causing diminished breakdown of ATP in the ischemic region, improved glycolytic flux, increased contractility of isolated ischemic heart muscle fibers and lowered tissue levels of lactate and free fatty acids. The mechanism underlying these improvements is not completely clear. In our experiments, ATP levels were higher in ischemic tissue in the diltiazem-treated dogs than in animals receiving no drug, perhaps because of diminished ATP consumption, which Fleckenstein[24] observed in the presence of several other calcium antagonists. Reductions in heart rate and mean aortic pressure may also play a minor role in preserving ATP levels in the ischemic region, and it is possible that decreased afterload is important. However, if these factors had played a major role, ATP levels probably would have risen in the nonischemic region as well.

Diminished hydrolysis of ATP, coupled with the lower levels of lactic acid found in the occluded region, would in turn reduce the tissue acidosis that normally accompanies ischemia. It has been shown that tissue pH levels frequently fall to between 6.3 and 6.5 during ischemia.[28,29] This decrease is normally ascribed to lactic acid accumulation, but recently Gevers[30] showed that the acidosis produced by the breakdown of ATP may play a greater role. The excess hydrogen ions produced interfere with several key metabolic processes, including glycolysis, because one of the rate-limiting enzymes in this pathway, phosphofructokinase, is pH-sensitive.[31] Therefore, a reduction in tissue acidosis would be expected to increase the activity of this enzyme. This change may explain the improved flux through phosphofructokinase demonstrated in our study.

Effect on contractility during ischemia: Administration of diltiazem also improved in vitro contractility of glycerinated muscle fibers isolated from the occluded region. Reductions in the maximal tension developed (P_0) and the maximal rate of tension development (dP/dt_{max}) in the diltiazem-treated dogs were only about half those found in the control group. The time to peak tension was also much less in the dogs receiving the drug. The difference in in vitro contractility between the two ischemic groups was large (37 to 49 percent), thus providing a suitable basis for comparison. The glycerinated fiber preparation used in our study is a measure of the integrity of the contractility apparatus, and thus increased contractility of ischemic fibers isolated from the diltiazem-treated animals indicates that

the calcium antagonist had a protective effect on the contractile mechanism in vivo. It is possible that a diltiazem-induced reduction in tissue acidosis, either through decreased ATP breakdown or lowered lactic acid levels, could reduce lysosomal activity and thus prevent damage to the contractile apparatus.[32,33]

Effect on mitochondria during ischemia: Administration of diltiazem did not protect the mitochondria from the effects of ischemia. The damage was nearly identical in mitochondria isolated from ischemic tissue in either group. The decline in oxygen consumption, which ranged from 15 to 30 percent of nonischemic levels, was similar in dogs receiving diltiazem and in those given no drug. Administration of the drug also did not lessen ischemia-induced reductions in respiratory control and mitochondrial calcium binding. Finally, although the absolute levels of free fatty acids were lower in the diltiazem-treated animals, the percent increases above nonischemic levels were roughly the same in both groups. Fatty acids, after esterification with coenzyme A, are oxidized to carbon dioxide and water within the mitochondrial matrix. Increases in tissue levels of fatty acids can occur during ischemia because of inhibition of the mitochondrial processes responsible for their breakdown, such as the beta oxidation pathway and the citric acid cycle. Reductions in these processes have previously been shown to accompany ischemia.[34,35]

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Reduction of Intimal Thickening in Canine Coronary Bypass Vein Grafts With Dipyridamole and Aspirin

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The potential benefit of platelet inhibitor drugs on coronary arterial bypass vein grafts was assessed in dogs with magnification-corrected angiographic luminal measurements and quantitative histologic evaluation of the vein grafts. There were 11 control animals and 11 animals treated with dipyridamole, 55 mg/day, plus aspirin, 325 mg/day. Eighteen animals with patent grafts were studied when electively killed 2, 4 or 6 months after grafting. At 14 days, there was greater angiographic narrowing in the most distal 1 cm of vein grafts in control than in treated dogs ($P < 0.01$). This same angiographic narrowing persisted in control dogs until they were killed ($P < 0.03$). Computer-assisted measurements of the entire area of intimal thickening were done on vein graft cross sections taken 1 cm from the distal anastomosis. The circumference of the vein grafts at the intimal-media junction was measured from the same section and the potential maximal luminal area calculated. The calculated luminal narrowing due to intimal thickening was greater in control than in treated dogs ($P < 0.03$). These data correlate well with the demonstrated angiographic narrowing. The findings indicate that the degree of early intimal thickening that persists 2 to 6 months postoperatively in canine coronary bypass vein grafts may be reduced by the platelet inhibitor combination of dipyridamole plus aspirin.

Aortocoronary bypass surgery with autologous saphenous vein grafts[1] is at present used widely in patients with coronary artery disease. A major limitation of this procedure is the occurrence of vein graft obstruction.[2,3] Pathologic studies of the aortocoronary saphenous vein grafts have revealed occluding thrombi in grafts from short-term survivors and intimal thickening resulting in occlusion in grafts from patients surviving for more than a month.[4–6]

There is now suggestive clinical and experimental evidence[7–9] that platelets may play an important role in the pathogenesis of early thrombotic graft occlusions. Moreover, experimental studies have linked platelets to the formation of intimal thickening in early atherosclerotic lesions,[10–13] and this thickening could be reduced or prevented by platelet inhibitors.[12] Because the morphologic characteristics of the intimal thickening of arterial atherosclerotic lesions are indistinguishable from those of the intimal thickening of the late vein graft occlusions,[4,14–16] it seems reasonable to consider that platelets may also play a critical role in the luminal narrowing of vein grafts. In this study, we attempted to determine whether platelet inhibitor drugs lessen the degree of intimal thickening, as judged angiographically and pathologically, in femoral vein coronary arterial bypass grafts in dogs.

Methods

Surgical procedure: With the use of cardiopulmonary bypass, 22 consecutive mongrel dogs weighing 17 to 22 kg underwent aorta-left anterior descending coronary arterial bypass grafting carried out through a thoracotomy in the fourth

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intercostal space. The unperfused undistended reversed right femoral leg vein was used for the bypass graft. In all animals the distal anastomosis, performed with the use of systemic hypothermia to 25°C, was made to the anterior descending coronary artery just distal to the first diagonal branch, with use of a running suture of 7-0 Prolene interrupted at two points. After completion of this distal anastomosis, a bulldog clamp was placed across the saphenous vein near the vein-coronary arterial anastomosis, the aorta was unclamped and rewarming was begun. A side-biting clamp was then placed on the ascending aorta, and the proximal anastomosis of vein to aorta was carried out with a running 6–0 Prolene stitch interrupted at two points. Before removal of the bulldog clamp on the distal portion of the vein, air was vented from the vein graft by aspiration through a 25 gauge needle. The heart was defibrillated with a single shock and, when suitable cardiac action had been reestablished, bypass was discontinued. The effect of heparin was reversed with protamine, a chest tube was placed and the chest was closed in routine fashion. During the operative procedure and the immediate postoperative period, arterial and venous pressures were monitored through the left internal mammary artery and left external jugular vein. When adequate spontaneous respiration occurred in the postoperative period, the chest tube and the monitoring catheters were removed, and the animals were returned to their cages.

Medication groups: The dogs were randomly assigned to one of two groups. In the control group 11 dogs underwent bypass grafting and received no medication other than systemic antibiotic drugs during the procedure and in the postoperative period. In the treated group 11 animals were given dipyridamole, 55 mg/day, for 2 days preoperatively (including the day of operation), 55 mg of dipyridamole the day after operation and then, starting 48 hours after operation dipyridamole, 55 mg/day plus aspirin 325 mg/day, and this regimen was continued until the dogs were killed. Pilot studies in our laboratory demonstrated that preoperative administration of dipyridamole with aspirin resulted in excessive intraoperative and postoperative bleeding. Consequently, in this study, aspirin was withheld until the postoperative period.

Of the 22 dogs that underwent aortocoronary vein bypass grafting, two dogs with patent grafts died of arrhythmias approximately 2 hours postoperatively. Technical problems compromised two additional grafts, and these specimens could not be justifiably used for comparative analysis. Eighteen dogs, nine treated and nine untreated, were included in our analyses. All dogs had a patent graft until the time of death.

Angiographic studies: Selective videoangiography of the aortocoronary vein graft was performed 14 days after operation and again just before the dog was killed. The animal, under light sodium pentobarbital anesthesia, was subjected to cardiac catheterization for the purpose of visualizing the bypass graft. It was positioned in a right anterior oblique position, and a no. 7F catheter was introduced through the left carotid artery and guided under fluoroscopic vision to the area of the aorta-vein anastomosis.At this point, an automated delivery system injected a constant volume of Renografin®, and a spot film was taken to demonstrate the anatomic location and the patency of the bypass graft. When suitable angiograms had been obtained, the catheter was removed, the artery ligated and the animal returned to its cage. The computer program described by Smith et al.[17,18] was used to determine the mean diameter of the most proximal and most distal 1 cm segments of each vein graft. Twenty equally spaced diameter measurements along each 1 cm segment were obtained to determine the mean diameter.

Pathologic studies: Each dog was killed 2, 4 or 6 months postoperatively. After formaldehyde fixation of the heart, the following tissue specimens were sampled for histologic examination: cross sections at multiple sites along the vein graft, sagittal sections across each anastomosis, cross sections of the native coronary artery distal to the graft-coronary arterial anastomosis and cross sections of the native coronary artery proximal to the ligature. Each specimen was paraffin-embedded, and consecutive 5 μ sections from each tissue block were processed for hematoxylin-eosin, Mallory-Heidenhain, and elastic van Gieson stains. All histologic sections were examined by an observer who had no prior knowledge of the animal groups.

To quantitate the intimal thickening, a photomicrograph of the elastic van Gieson–stained cross section taken 1 cm proximal to the distal anastomosis was made at a magnification 10 times the original. A graduated microscopic eyepiece grid (Bausch and Lomb, Whipple Disc 31-16-21) of known area was similarly photographed. The photograph of the grid served as a standard for linear and area measurements. The pathologist marked the intima-medial junction directly on the photographs with a fine-point ink pen. Using an operator-interactive computer-controlled system for high fidelity digitization and analysis of biomedical images,[19] we measured the area of the outlined image by tracing out the border of the intimal-medial junction using a light pen on-line to the computer. The area of the image bordering on the luminal margin of the vessel was also determined and subtracted from the area subtended by the intimal-medial junction (Fig. 1). The resultant area was a measure of intimal thickening.

The degree of luminal narrowing caused by the intimal thickening was calculated using the absolute pictorial area of intimal thickening from each section and dividing this by the calculated maximal potential luminal area from each respective section. This decimal fraction was then multiplied by 100 percent to determine the percent graft narrowing

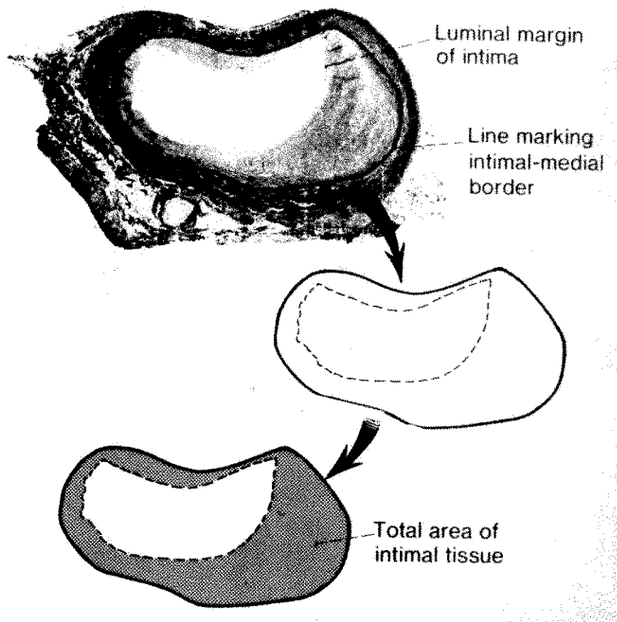


FIGURE 1. Photomicrograph (**top**) and diagrams (**center** and **bottom**) of vein graft cross section. To compute the total area of intimal tissue (**shaded**), the area within the luminal margin was subtracted from the area within the intimal-medial border.

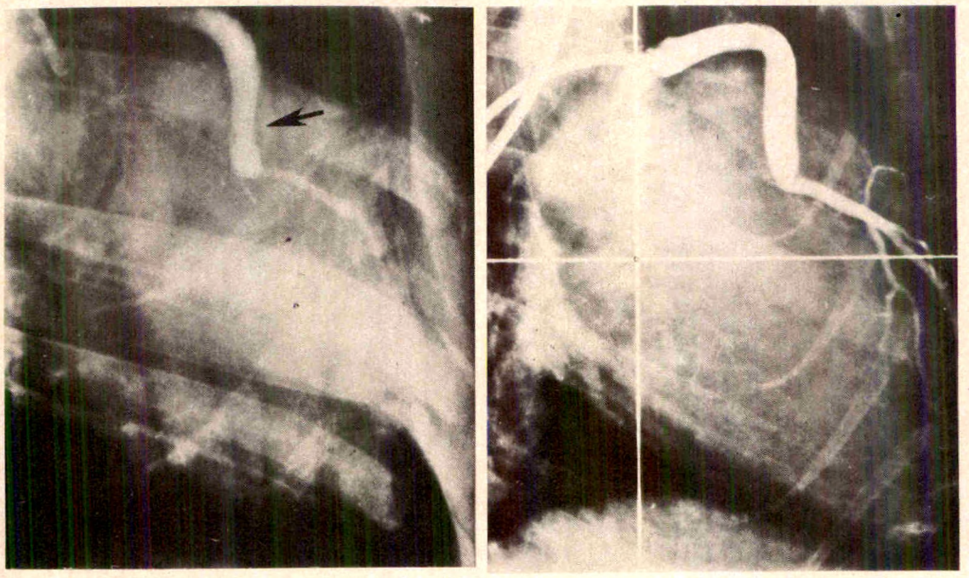


FIGURE 2. X-ray films (right anterior oblique projection) of vein grafts from an untreated (**left**) and a treated (**right**) dog. Note the luminal narrowing in the distal portion of the vein graft from the untreated dog (**arrow**).

secondary to intimal thickening. The calculated maximal potential luminal area was derived from a precise measurement of the graft circumference at the intimal-medial junction. Because the maximal area of any image of known circumference is identical to the area of a circle of the same circumference, we used the formulas that apply to circles (circumference = $2\pi r$; area = $2\pi r^2$) to determine the maximal potential luminal area.

TABLE I

Postoperative Mean Diameter of Graft Segments (mm)

Dog Group	Proximal		Distal	
	14 Days	on Death	14 Days	on Death
Untreated	6.30 ± 0.66*	6.44 ± 0.41†	5.10 ± 0.97‡	5.78 ± 1.95§
Treated	6.82 ± 0.41*	7.55 ± 0.56†	7.10 ± 1.00‡	7.55 ± 1.05§

* Difference not significant; † P (probability) <0.001; ‡ P <0.01; § P < 0.03.

Results

Angiographic findings: In the distal vein graft segments, 14 days after operation, the mean diameter was significantly smaller (P <0.01) in the untreated than in the treated dogs (Table I, Fig. 2). When the same comparisons were made just before the dogs were killed, the distal segments again were narrower (P <0.03) in the untreated than in the treated dogs. The proximal vein graft segments at 14 days after operation were not significantly different in untreated and treated dogs. However, the late studies demonstrated a significant difference (P <0.001) (Table I) because, with time, the absolute mean diameter of the proximal segment in the treated animals increased from 6.82 ± 0.41 to 7.55 ± 0.56 mm (P <0.01), whereas no significant increase occurred in the untreated dogs.

Pathologic findings: Inspection of the hearts before fixation revealed the aortic anastomosis to be widely

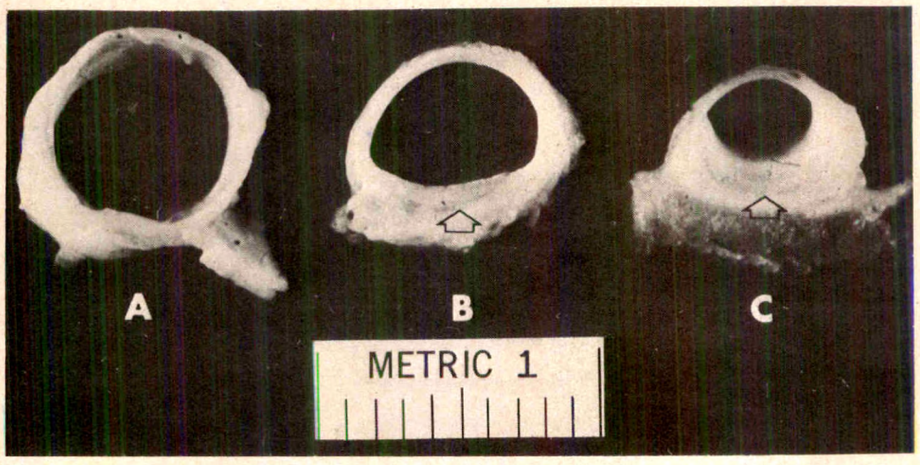


FIGURE 3. Cross-sectional 1 mm rings from an untreated dog. **A**, 1 cm from the aortic anastomosis; **B**, mid graft level; **C**, 1 cm from the graft-coronary arterial anastomosis. Note the degree of intimal thickening in sections **B** and **C**, as indicated by **arrows.**

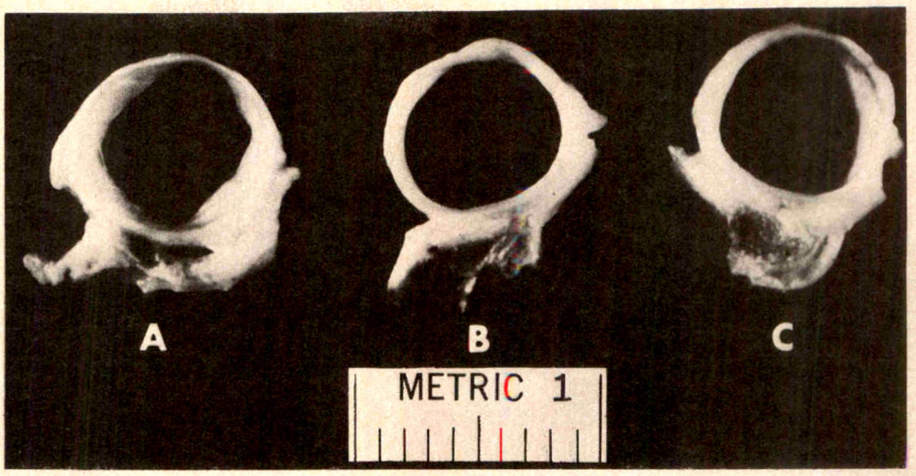


FIGURE 4. Cross-sectional 1 mm rings from a treated dog. **A**, 1 cm from the aortic anastomosis; **B**, mid graft level; **C**, 1 cm from the graft-coronary arterial anastomosis. There is little or no intimal thickening.

patent in all animals. On histologic examination, intimal proliferation was uniformly present to a greater or lesser degree in all vein grafts beginning at the aortic anastomosis and extending 1 to 2 mm into the coronary artery. Beyond this the coronary artery was normal. The intimal thickening consisted of varying combinations of subendothelial proliferation of smooth muscle cells (myointimal cells), deposition of extra cell fibrocollagenous connective tissue and stainable proteoglycens. Significant asymmetric intimal thickening was present in seven of nine untreated animals (Fig. 3). In the treated group only two of the nine had intimal thickening similar in severity to that of the untreated group; the remaining seven had only minimal thickening (Fig. 4).

Quantitative histologic examination of the thickened intima from the vein graft cross sections taken 8 to 10 mm proximal to the graft-coronary arterial anastomoses revealed 37.3 ± 7.6 (standard error) percent luminal narrowing in the untreated grafts compared with 15.5 ± 4.55 percent luminal narrowing in the treated grafts (Fig. 5). This difference in degree of intimal thickening was statistically significant ($P < 0.03$).

Discussion

Platelet inhibitor drugs, graft narrowing and intimal thickening: One of the major limitations of aortocoronary bypass surgery with autologous saphenous vein grafts is the occurrence of occlusion of the grafts secondary to thrombosis or intimal proliferation. Because platelets appear to play a role in the process of vascular occlusive disease we tested the possible preventive effects of a platelet inhibitor drug regimen in a homogeneous group of dogs with no known risk factors for cardiovascular disease. The data obtained from these studies demonstrate that treatment with the regimen of dipyridamole plus aspirin, at dosages comparable with those used in human beings,[20] significantly decreased the amount of intimal proliferation in coronary bypass grafts. Angiographic measurement of mean diameters in the most proximal and the most distal 1 cm segment of each vein graft was thought to represent best the diameters of the lumens at either end of the graft. The lumen within the most proximal 1 cm vein graft segment was fairly uniform in diameter, and any one diameter within the segment approximated that segment's mean diameter. Within the distal 1 cm segment,

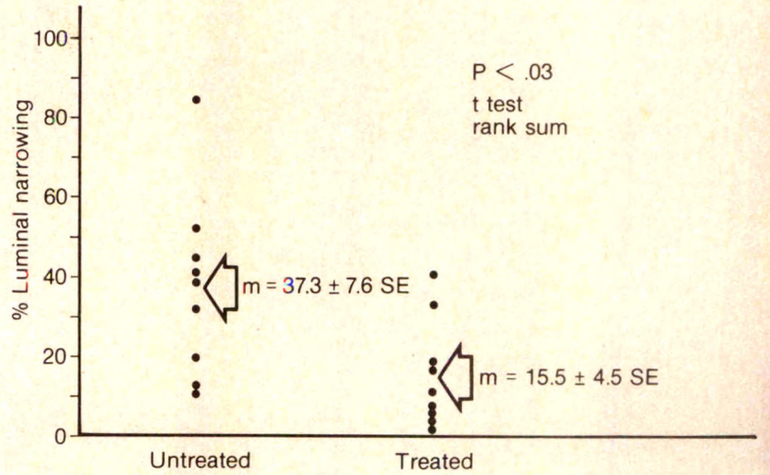


FIGURE 5. Percent graft luminal narrowing 8 to 10 mm from the graft-coronary arterial anastomosis in untreated and treated dogs. m = mean; SE = standard error; P = probability.

particularly in untreated animals, the graft lumen tended to narrow progressively. Had we selected the most narrowed diameter rather than the mean diameter within this segment then the differences in diameter noted angiographically from the proximal to the distal segment and between groups would have been even more striking. Nevertheless, distal graft narrowing was significantly different in the untreated and treated animals.

For the quantitative determination of intimal thickening, we arbitrarily selected the cross section taken 1 cm from the distal anastomosis for the measurement of intimal thickening. This site was selected because the distal ends were most prone to the development of intimal thickening. The vein graft intimal thickening seen in our studies was indistinguishable from the arterial lesion of intimal smooth muscle proliferation seen in human beings.[4,16]

In the calculation of percent luminal narrowing a bias is introduced that minimizes the difference between the untreated and treated animals. The measurement of maximal potential luminal area is used in the denominator of this calculation, and one known factor influenced it. The vein grafts from untreated animals were grossly more thin-walled and distensible in vivo; thus, the measurement of maximal potential luminal area is an underestimate in this group. In light of this factor, the luminal narrowing would be less than calculated.

Clinical implications: It is estimated that in this country alone, at least 50,000 patients undergo aortocoronary bypass surgery with saphenous vein grafts every year. New therapeutic approaches are needed to reduce the significant incidence of graft occlusion in these patients. Our study suggests that the drug regimen of dipyridamole plus aspirin can improve the graft patency rates in dogs. Therefore, the design of clinical trials to test the protective effect of this drug combination is now fully justified in patients undergoing aortocoronary bypass surgery.

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Canine Electrophysiology of Encainide, a New Antiarrhythmic Drug

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Encainide, a new benzanillide derivative with high potency and a good therapeutic/toxic ratio, was evaluated with the use of standard His bundle recording techniques to determine its effects on the cardiac conduction system in closed chest animals. Twenty mongrel dogs weighing 18 to 29 kg were anesthetized with 4 percent chloralose and classified into groups: group 1, a control group and groups 2, 3, and 4, which were given 0.3, 0.9 and 2.7 mg/kg body weight, respectively, of encainide in an intravenous infusion over a 15 minute period. Plasma concentration, blood pressure, surface electrocardiogram and atrial and His bundle electrograms were recorded before, during and after drug infusion for a total of 120 minutes. Heart rate, A-H and H-V intervals, the QRS complex and Q-Tc interval were measured every 5 minutes during sinus rhythm and with constant atrial pacing. In addition, sinus nodal recovery time and atrial, atrioventricular (A-V) nodal and left ventricular refractory periods were measured before and immediately after infusion and every 30 minutes for 2 hours. Peak plasma concentration averaged 450 ng/ml in group 2, 1,300 ng/ml in group 3 and 4,000 ng/ml in group 4. Blood pressure was not altered at any dose level throughout the study. The QRS complex and H-V interval were significantly prolonged ($P < 0.005$) at doses of 0.9 mg/kg and greater. These effects correlated well with plasma concentration. There was no significant change in heart rate, corrected sinus nodal recovery time, A-H interval, Q-Tc interval atrial, A-V nodal or left ventricular refractory period. It is concluded that, unlike other antiarrhythmic agents, encainide prolongs His-Purkinje system conduction without significantly affecting conduction or refractoriness of other parts of the cardiac conduction system in animals.

Encainide is a new benzanillide derivative chemically identified as [4-methoxy-2″ (1-methyl-2-piperidyl ethyl) benzanillide] hydrochloride with laboratory-documented antiarrhythmic action. Its chemical structure does not resemble that of any of the known antiarrhythmic drugs (Fig. 1). The agent was selected from a series of chemically related structures on the basis of its antiarrhythmic efficacy in various animal models.[1–3] It was also tested preliminarily in human volunteers with oral and intravenous doses ranging from 0.25 to 2.0 mg/kg body weight and showed a high therapeutic/toxic ratio. In order to expand the clinical studies with encainide, it is necessary to define its electrophysiologic properties in the cardiac conduction system. Accordingly, in this study we attempted to determine the acute effect of intravenously administered encainide on the cardiac conduction system in animals with the use of standard His bundle recording techniques.

Methods

Study Population

The experiments were conducted with a closed chest technique in 20 mongrel dogs ranging in weight from 18 to 29 kg. The animals were anesthetized with a

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4–methoxy–2'–[2–(1–methyl–2–piperidyl) ethyl] benzanilide hydrochloride

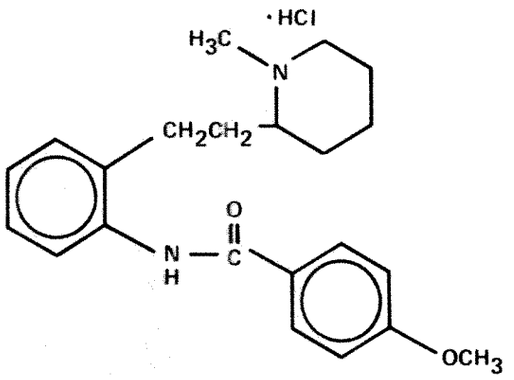


FIGURE 1. Structural formula of encainide.

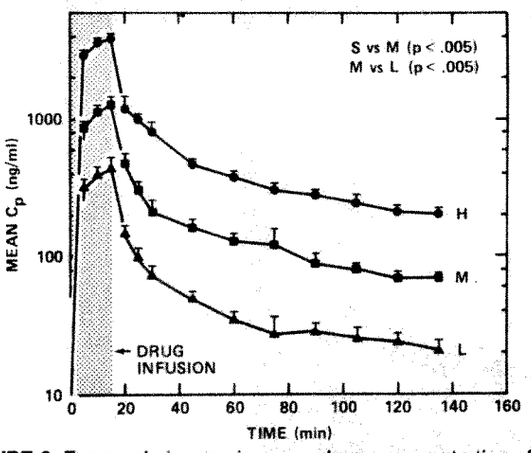


FIGURE 2. Temporal changes in mean plasma concentration of encainide. Cp = plasma concentration; L = large dose = 2.7 mg/kgl (no. = 7); M = medium dose = 0.9 mg/kg (no. = 4); p = probability; S = small dose = 0.3 mg/kg (no. = 4). The **hatched area** indicates the 15 minute drug infusion period. Statistical intergroup differences were evaluated at the end of the 15 minute infusion period (T_{15}).

4 percent solution of alpha chloralose in polyethylene glycol, 5 cc/kg initially, and additional 1 cc/kg doses as required to maintain a constant level of anesthesia. The dogs were intubated with a cuffed endotracheal tube and ventilated with humidified room air, using a Harvard pump. Arterial blood gas tensions were determined using a Corning model 165 Blood Gas Analyzer. The depth and rate of respiration were adjusted so as to maintain an arterial oxygen tension over 72 mm Hg and pH between 7.35 and 7.44. The temperature of the animal was maintained at 37°C using a thermal blanket. A catheter was inserted into the left femoral artery to monitor the systemic arterial blood pressure with a Statham P23Db transducer and to allow access for blood gas sampling and determination of plasma drug concentration. The right femoral vein was exposed and cannulated for infusion of encainide and chloralose.

Electrophysiologic Methods

The right and left carotid arteries and right internal jugular veins were exposed with a cutdown procedure. A no. 7 tripolar recording catheter was advanced through an arteriotomy in the right external carotid artery until resistance was met at the aortic valve. The catheter was then manipulated until a satisfactory His bundle electrogram was obtained. A no. 7 quadripolar pacing and recording catheter was advanced to the right atrium through the right internal jugular vein and positioned so as to obtain atrial pacing and recording. A no. 7 quadripolar electrode catheter was positioned in the left ventricle through a cutdown in the left external carotid artery.

Surface electrocardiographic leads I, II and aVF were recorded simultaneously with atrial, ventricular and His bundle electrograms. Intracardiac signals were filtered at frequencies of 50 to 500 hertz through the alternative current input of a Hewlett-Packard 88-11A bioelectric amplifier, and the data were displayed on a switched-beam oscilloscope and recorded on Kodak light-sensitive paper with a Honeywell 1508 write-out at 100 mm/sec. In addition, the H-V intervals were displayed on a Tektronix 7623A storage oscilloscope at a sweep speed of 5 or 10 msec/cm and recorded on Polaroid® 3,000 speed, type 107 film. Atrial and ventricular pacing stimuli of 2 msec duration were delivered by a Tektronix pulse generator through an electrical isolation unit at twice the diastolic threshold.

Measurements: *After instrumentation, the following measurements were obtained:* plasma concentration, blood pressure, conduction intervals (A-H, H-V, QRS and Q-T intervals) measured during sinus rhythm and with constant atrial pacing at a cycle length of 50 to 100 msec below the spontaneous cycle length. In addition, the corrected sinus nodal recovery time, Wenckebach cycle length and atrial, atrioventricular atrial, (A-V) nodal and left ventricular refractory periods were determined.

The H-V interval was measured from a rapid sweep oscilloscopic display of the His bundle electrogram. To avoid confusing the onset of His bundle activation with baseline instability, measurements were taken from the onset of the first rapid His deflection to the onset of the local ventricular electrogram. This oscilloscopic method for H-V measurement was used to increase resolution and accuracy. In addition, the relation of onset of the local ventricular electrogram in the His bundle lead to the earliest surface QRS deflection recorded on paper at 100 mm/sec was evaluated in each animal before and after encainide, and no change was seen. This finding shows that this method did not measure a change in intraventricular or selective right bundle branch conduction velocity rather than true His-Purkinje system conduction. The sinus cycle length was averaged from 10 consecutive sinus beats. The QRS and Q-T intervals were measured from the surface electrocardiogram. The Q-T interval was corrected to a cycle length of 1 second by the formula: $Q\text{-}T_c = Q\text{-}T/\sqrt{R\text{-}R}$.

The sinus nodal recovery time was measured as the longest sinus pause after atrial pacing at cycle lengths of 400, 350, 300 and 250 msec. Each rapid pacing episode was separated from the subsequent period by a 60 second rest. The corrected sinus nodal recovery time ($SNRT_c$) was calculated according to the following formula: $SNRT_c = SNRT - (R\text{-}R)$. The Wenckebach cycle length was defined as the longest atrial pacing cycle length at which A-V nodal Wenckebach conduction consistently occurred, determined to the nearest 10 mm sec.

Programmed premature extra stimuli were used to evaluate refractory periods.[4] The atrial effective refractory period and the A-V nodal functional and effective refractory periods were determined during atrial pacing at the basic cycle length

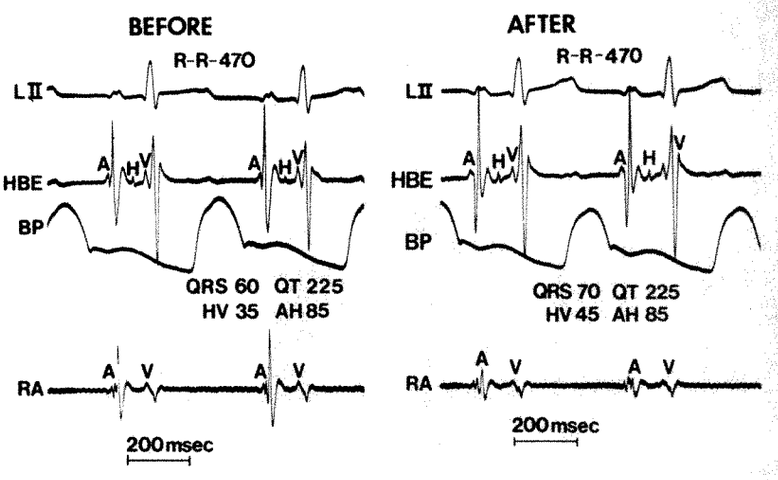


FIGURE 3. Recordings during spontaneous sinus rhythm (100 mm/sec) before and after infusion of 0.9 mg/kg of encainide in one animal. **From top to bottom,** L II = surface electrocardiographic lead II; HBE = His bundle electrogram; BP = blood pressure; RA = right atrial electrogram. A = atrial potential; H = His bundle potential; V = ventricular potential. The QRS duration was 60 msec before and 70 msec after drug infusion. The H-V interval was 35 msec before and 45 msec after drug infusion; no change occurred in the R-R interval (470 msec), Q-T (225 msec) or A-H (85 msec) interval.

and measured to the nearest 10 msec, using techniques and definitions previously described.[5] The left ventricular effective refractory period was measured during constant atrial pacing by programmed premature left ventricular extrastimuli (S_2) introduced after every eight paced basic drive beats (S_1). The longest S_1–S_2 interval at which S_2 consistently failed to capture the ventricle was considered the effective refractory period of the left ventricle. The sequence of stimuli was programmed on a digital stimulator (WPI, New Haven).

Drug infusion: *The animals were separated into four groups:* A control group of five dogs received a 15 minute intravenous infusion of normal saline solution. A "small" dose group of four dogs received 0.3 mg/kg of encainide; a "medium" dose group of four dogs received 0.9 mg/kg and a "large" dose group of seven dogs received 2.7 mg/kg of encainide. In every case, the total dose of drug was infused intravenously over 15 minutes by a Harvard pump.

With radioimmunoassay technique, the plasma concentration of encainide was measured every 5 minutes for the first 30 minutes after the start of infusion and every 15 minutes thereafter for a total of 2 hours. Blood pressure and electrophysiologic measurements were repeated after the end of infusion and every 30 minutes thereafter for a total of 2 hours. In addition, blood pressure and conduction interval measurements (sinus cycle length, A-H, H-V, QRS and Q-T_c intervals) were measured every 15 minutes throughout the study.

Statistical analysis: A one way analysis of variance was used to determine the statistical significance of the maximal changes from control state observed after encainide infusion. When the F value was found statistically significant, Student's unpaired *t* tests were used to evaluate differences between doses. Linear regression curves were used to evaluate the relation between peak plasma concentration and maximal electrophysiologic effects after infusion of encainide. Standard deviations are expressed throughout.

Results

Encainide plasma concentration: Figure 2 shows the plasma concentration of encainide during and after 15 minutes of infusion of 0.3, 0.9 and 2.7 mg/kg of the drug. Peak plasma concentration was reached at the end of the infusion in each animal and averaged 460 ± 150, 1,300 ± 310 and 4,100 ± 190 ng/ml for the small, medium and large doses, respectively. After the end of infusion the decrease in plasma concentration was biexponential: The rapid distribution phase took about 15 minutes and the elimination half-life for each of the three dose levels was estimated graphically on a semilogarithmic paper to be approximately 1.5 hours.

Electrophysiologic Effects

Encainide significantly prolonged the H-V interval and QRS duration at doses of 0.9 mg/kg and greater (Fig. 3). These prolongations were not accompanied by significant changes in sinus cycle length, blood pressure or A-H or Q-T_c interval. Figure 4 shows an example of the Polaroid® pictures obtained from the oscilloscopic display of the H-V interval before and after infusion of 2.7 mg/kg of encainide in one animal. Because peak plasma concentration coincided with the end of infusion (T_{15}), percent changes from baseline at T_{15} were calculated and averaged for each dose group and compared with the control value (Table I).

Effect on His-Purkinje system and ventricles: Highly significant increases in H-V interval and QRS duration were noted after encainide infusion ($F = 37.36$, $P < 0.001$) and $F = 29.87$, $P < 0.001$, respectively). No significant changes were noted in ventricular repolarization (Q-T_c interval) or ventricular refractoriness. The refractory period of the His Purkinje system could not be determined because preferential delay or block did not occur in any animal below the level of the His bundle.

Figure 5 shows the mean maximal percent increase in the H-V interval and QRS duration observed at T_{15} in each of the three drug groups. In the small dose group, encainide produced an insignificant increase in both variables. In the medium dose group the increases in the H-V interval and QRS duration were 31 and 15 percent respectively. These increases were significantly different from those observed at the small dose level ($P < 0.001$ for the H-V interval and $P < 0.005$ for the QRS complex). The mean maximal percent increase in these variables reached 48 and 39 percent, respectively, in the large dose group. These increases were also significantly different from those observed at the medium dose level

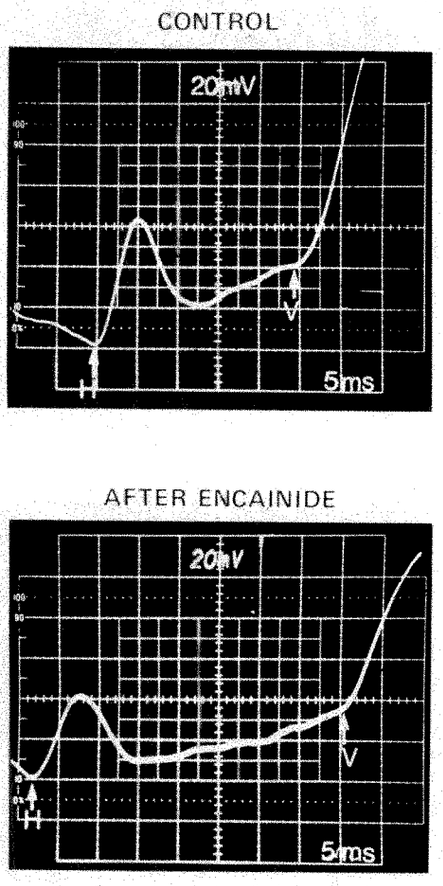


FIGURE 4. Oscilloscopic recording (5 msec/cm) of the H-V interval measured during constant atrial pacing before (CONTROL) and after infusion of 2.7 mg/kg of encainide. H = His bundle potential; ms = milliseconds; V = ventricular potential.

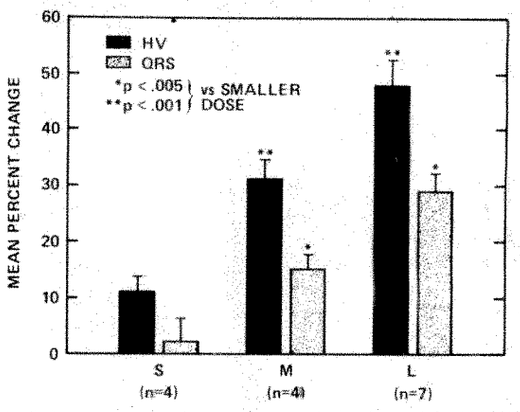


FIGURE 5. Mean percent change from control values of the H-V interval and QRS duration measured at the end of encainide infusion (T_{15}) in dogs receiving a small (S) dose of 0.3 mg/kg (11 and 2 percent, respectively), a medium (M) dose of 0.9 mg/kg (31 and 15 percent, respectively) and a large (L) dose of 2.7 mg/kg (48 and 29 percent, respectively). n = number of dogs; p = probability.

(P <0.001 for the H-V interval and P <0.005 for the QRS complex).

Figure 6, top shows the mean changes in the H-V interval from basal values during the entire period of the study in control animals and in the small, medium and large dose groups. Although the H-V interval did not change during the entire period of observation in control animals, it showed maximal increases at T_{15} and an exponential return toward basal values in all three drug groups. The same pattern of variation was observed for the QRS duration (Fig. 6, bottom).

Effect on sinus node: The average change in heart rate at T_{15} did not exceed 2 percent in control animal

TABLE I

Mean Percent Change of Electrophysiologic Variables at the End of a 15 Minute Infusion of Encainide

Variable	Control	Small Dose	Medium Dose	Large Dose	Analysis of Variance (F)
no. of dogs	5	4	4	7	
Effect on sinus node					
Heart rate	2 ± 2	3 ± 8	−7 ± 9	2 ± 8	1.27 NS
Max $SNRT_c$	32 ± 47	33 ± 64	58 ± 154	−1 ± 64	0.44 NS
Effect on atrium					
Atrial ERP	0 ± 0	13 ± 8	9 ± 13	7 ± 12	1.10 NS
Effect on A-V node					
1. Conduction					
Paced A-H	−2 ± 9	−3 ± 9	13 ± 5	7 ± 9	2.89 NS
Wenckebach cycle length	1 ± 2	3 ± 12	7 ± 9	12 ± 10	1.20 NS
2. Refractoriness					
FRP	−1 ± 3	1 ± 6	6 ± 3	2 ± 3	1.89 NS
ERP	−2 ± 4	16 ± 8	7 ± 14	5 ± 8	2.16 NS
Effect on His-Purkinje system and ventricles					
1. Conduction					
Paced H-V	0 ± 0	11 ± 5	31 ± 7	48 ± 12	37.36*
Paced QRS	0 ± 0	2 ± 8	15 ± 5	29 ± 7	29.87*
2. Repolarization					
Q-Tc	−1 ± 6	1 ± 5	1.5 ± 6	4 ± 4	0.92 NS
3. Refactoriness					
Left ventricular ERP	0 ± 0	—	—	0 ± 0	—

* Probability (P) < 0.001.

A-V = atrioventricular; ERP = effective refractory period; FRP = functional refractory period; NS = not significant $SNRT_c$ = corrected sinus node recovery time.

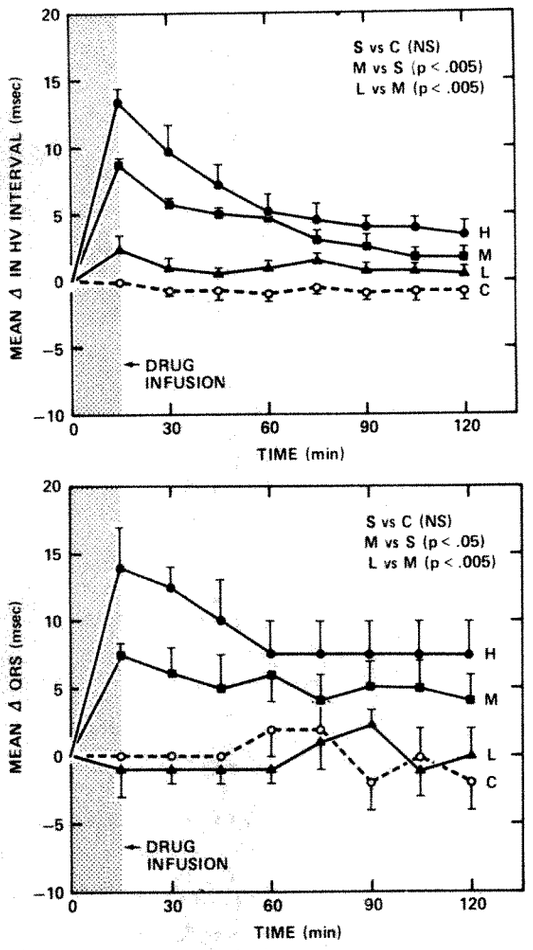


FIGURE 6. Temporal changes (Δ) in the mean H-V interval **(top)** and QRS duration **(bottom)** in five control animals (C) and four animals receiving a small (S) dose (0.3 mg/kg), four receiving a medium (M) dose (0.9 mg/kg) and seven receiving a large dose (L) (2.7 mg/kg) of encainide. Statistical intergroup differences were evaluated at the end of the infusion period (T_{15}). NS = not significant; p = probability.

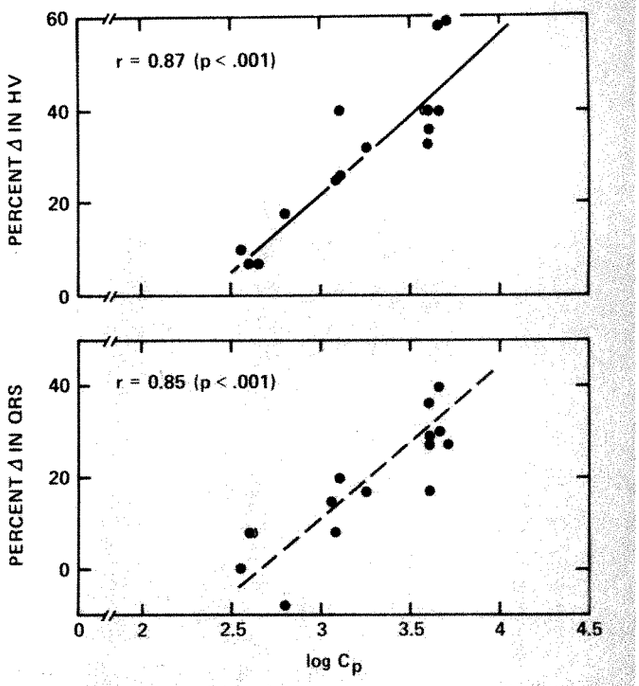


FIGURE 7. Linear regression between the percent changes (Δ) in the H-V interval and QRS duration and the log plasma concentration (C_p) of encainide measured at the end of the infusion period (T_{15}) in all 15 animals receiving the drug. p = probability; r = correlation coefficient.

and increased by 3 and 2 percent, respectively, in the small and large dose groups and decreased by 7 percent in the medium dose group. These changes were not statistically significant. The changes in maximal sinus nodal recovery time showed marked intragroup variations and did not reach statistical significance (F = 0.44) (Table I).

Effect on atrium: No change in the atrial effective refractory period was observed at T_{15} in control animals. The mean percent increase was 15 ± 8 msec in the small dose group, 9 ± 13 msec in the medium dose group and 7 ± 12 msec in the large dose group. These changes were not statistically significant (F = 1.10) (Table I).

Effect on A-V nodal conduction: The mean percent change in the A-H interval measured during constant atrial pacing was −2 ± 9 in control animals, −3 ± 9 in the small dose group, 15 ± 5 in the medium dose group and 7 ± 9 in the large dose group, but again these changes did not reach statistical significance (F = 2.89, P = 0.25). The average change in Wenckebach cycle length did not exceed 1 percent in control animals. However, animals receiving encainide showed marked intragroup variations from basal values, but the average percent increase at T_{15} for all dose levels remained nonsignificant (F = 1.20) (Table I).

Effect on A-V nodal refractoriness: The A-V nodal functional refractory period remained virtually unaltered at T_{15} in control animals as well as in animals receiving each of the three doses of encainide (F = 1.89, difference not significant). In contrast the A-V nodal effective refractory period showed wide intragroup variations in animals receiving encainide as compared with control animals. However, none of the average changes, reached statistical significance (F = 2.16) (Table I).

Correlations of electrophysiologic changes with plasma concentration of encainide: Figure 7 shows the correlation between the percent increase in the H-V interval and QRS duration at T_{15} with the peak plasma concentration of encainide at the same time. For both the H-V interval and QRS duration the correlation with the log plasma concentration was linear and highly significant: r = 0.87 (P <0.001) for the H-V interval and r = 0.85 (P <0.001) for the QRS duration. None of the other electrophysiologic variables measured correlated significantly with the plasma concentration.

Effect on blood pressure: The average changes in mean arterial blood pressure at T_{15} did not exceed 1 percent in control animals. The average mean arterial blood pressure increased by 2 percent in small and large

dose groups and decreased by 1 percent in the medium dose group. These changes were not statistically significant.

Discussion

We have studied the electrophysiologic effects of encainide in closed chest animals at three doses (0.3, 0.9 and 2.7 mg/kg, respectively) that, on the basis of previous observations,[1,2] were believed to cover a wide spectrum of plasma concentration ranging from below to well above therapeutic levels. In our study, encainide significantly delayed His-Purkinje system and intraventricular conduction at doses of 0.9 mg/kg and greater (Fig. 5). This delay was highly correlated with the plasma concentration achieved in these dogs (Fig. 7). Whether this delay reflects a selective action on the specialized conduction fibers of the His-Purkinje system or an effect on ventricular muscle conduction as well could not be determined in our study. However, this marked effect on His-Purkinje conduction was not associated with a significant effect on ventricular repolarization or refractoriness. Gibson et al.[3] found similar effects of encainide on transmembrane potentials of canine Purkinje fibers. Encainide did not significantly change blood pressure, heart rate or any of the other electrophysiologic variables measured (Table I).

Comparison with other antiarrhythmic agents: Encainide resembles the class I antiarrhythmic agents (quinidine, procainamide, disopyramide) that also significantly prolong conduction in the His-Purkinje system,[6–8] an effect that is believed to be closely associated with their antiarrhythmic potency.[9] However, encainide, differs from class I drugs in that it does not significantly prolong the ventricular effective refractory period or the Q-T_c interval, two effects that are consistently observed with therapeutic doses of class I drugs.[6–8] Furthermore, quinidine-like drugs are reported to prolong the atrial effective refractory period. Whereas this effect was observed in some of our animals at all dose levels, the mean percent increase in the atrial effective retractory period at various dose levels did not reach statistical significance and was not significantly correlated with plasma concentration (Table I). Quinidine and quinidine-like drugs lower the blood pressure and accelerate heart rate, either reflexly or by a vagolytic effect. These effects were not observed in our study at any dose level of encainide. The electrophysiologic effects of encainide as noted in our study do not resemble those of lidocaine,[10] tocainide,[5,11] beta adrenergic blocking agents[12,13] or other newly described antiarrhythmic drugs.[14]

Clinical implications: Although there are only limited clinical data on encainide, our electrophysiologic studies permit us to speculate on its possible clinical role. Because encainide significantly prolongs His-Purkinje system conduction it can be speculated that this is a mechanism by which it prevents or abolishes reentrant ventricular arrhythmias. Gibson et al. also found that encainide depresses automaticity in His-Purkinje canine myocardial fibers,[3] an effect that is believed to be common to most antiarrhythmic drugs.[10]

Encainide has little if any effect on A-V nodal conduction and refractoriness and therefore should be safe to combine with beta blocking agents or calcium antagonists. Encainide may prove to be of use in patients in whom slowing of the A-V nodal conduction is undesirable. Encainide should probably not be used in conjunction with quinidine-like drugs because they significantly prolong the H-V interval and QRS duration and this combination might represent a risk, especially in patients with disturbances of His-Purkinje conduction.

Acknowledgment

We thank Dr. Robert Mayol from the Mead Johnson Research Center, Evansville, Indiana for developing the radioimmunoassay technique of measuring encainide plasma concentration and Dr. Jeffrey Travis from the Orange County Institute, Newport Beach, California for performing the assay. We are also indebted to Robert Kernoff and George Snidow for technical assistance and to Dorothy Potter for typing the manuscript.

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Effects of Thioridazine (Mellaril) on Ventricular Electrophysiologic Properties

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The effects of therapeutic and toxic doses of thioridazine (Mellaril) (10 and 50 mg/kg body weight, respectively) on ventricular electrophysiologic properties were studied in 12 anesthetized dogs. Threshold pacing currents (diastolic threshold), effective refractory period and conduction time were significantly increased, and idioventricular automaticity was suppressed after administration of 10 mg/kg of thioridazine; the effects were much more pronounced after administration of 50 mg/kg. Rapidly repetitive responses or tachycardia could be induced in the ventricle by two early premature beats in 9 of the 12 dogs after the 50 mg/kg dose, but they did not occur before drug administration or after the 10 mg/kg dose. These results indicate that the antiarrhythmic and arrhythmogenic effects of thioridazine are dose-dependent and that careful monitoring with frequent electrocardiograms is needed for patients receiving large doses of this drug.

The antiarrhythmic properties of thioridazine (Mellaril®) and other phenothiazine derivatives have been observed in animal experiments,[1–4] and the arrhythmogenic effects of these agents have also been observed clinically.[5–9] The arrhythmogenic complications were reported in relatively young persons who often had no apparent heart disease. Phenothiazine derivatives are widely used psychotropic agents, but electrocardiographic monitoring has not been frequent enough to elucidate the nature of their cardiac effects in man. Because the reported fatal complications occurred in patients taking relatively large doses of phenothiazines, the arrhythmogenic effects might be dose-dependent. This study was conducted to test the effects of therapeutic and toxic doses of thioridazine on the electrophysiologic properties of canine ventricles.

Methods

Experimental procedure: Experiments were performed in 12 mongrel dogs anesthetized by intravenous injection of sodium pentobarbital, 30 to 35 mg/kg body weight. Under artificial respiration, the thorax was opened in the mid line and the heart was cradled in the opened pericardium. A femoral vein was cannulated for injection of thioridazine, and a femoral artery was cannulated to record the arterial pressure. Complete atrioventricular (A-V) block and the resultant idioventricular rhythm were produced by destroying the His bundle with an electric cautery knife, as described in our previous study.[10] This model was chosen to study the effect of thioridazine on idioventricular automaticity.

A pair of stimulating electrodes was attached to the anterior surface of the right ventricle, and a pair of recording electrodes was attached at a distance of 50 mm. Lead II electrograms, local right ventricular electrograms and the artifacts of stimuli delivered to the right ventricular stimulating site were recorded on an Electronics for Medicine recorder. Patterns of basic and premature stimuli were programmed using a variable interval generator. The output of the interval generator triggered a Tektronix pulse generator that delivered rectangular pulses of 2 msec duration to the stimulating electrodes. The stimuli were also displayed on an oscilloscope and calibrated by means of a Tektronix current probe amplifier.

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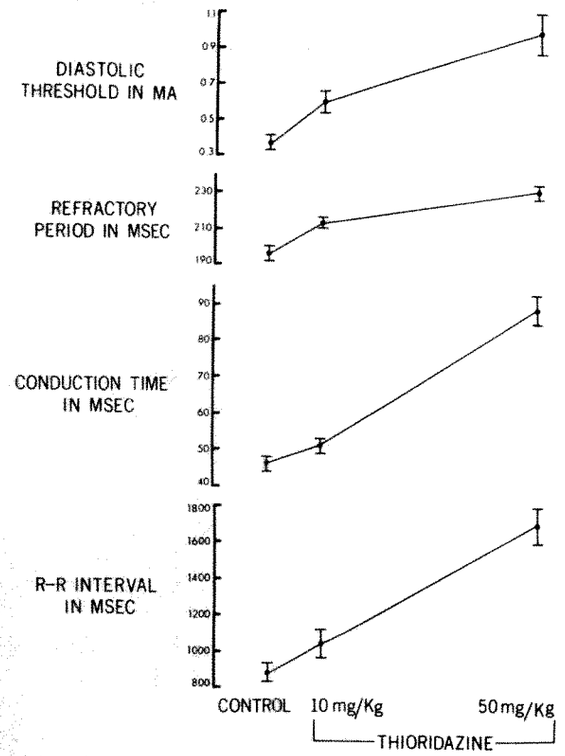


FIGURE 1. Effects of thioridazine in two doses on diastolic threshold, effective refractory period, conduction time and the R-R interval. The values are means ± standard error. MA = miliamperes.

Electrophysiologic measurements: The threshold pacing current or diastolic threshold was determined by applying basic stimuli (S_1) of variable current intensities to the right ventricle at a cycle length of 400 to 500 msec, and the right ventricle was then paced by the basic S_1 at twice the diastolic threshold. The effective refractory period was determined by using a premature stimulus (S_2) delivered at variable intervals after every 12th basic S_1. The right ventricular local electrogram and the lead II electrocardiogram were used to indicate the success or failure of S_2 in evoking a propagated response. The interval between S_1 and the earliest successful S_2 was recorded as an estimate of the effective refractory period. Ventricular conduction time was determined by measuring the interval between S_1 and its response at the right ventricular recording site. The destruction of the His bundle resulted in A-V dissociation with wide QRS complexes indicating idioventricular rather than A-V junctional rhythm. Idioventricular automaticity was determined by measuring R-R intervals of idioventricular rhythm. Ventricular vulnerability to arrhythmia was tested by applying two premature stimuli (S_2 and S_3) that produce two successive premature beats at the earliest possible intervals. Our earlier studies[10,11] showed that rapidly repetitive responses could be regularly induced by two early premature beats in the ventricle with increased vulnerability to arrhythmias.

Drug administration: A solution of thioridazine was prepared by dissolving the drug in normal saline solution to a concentration of 50 mg/ml. In each animal after control observations were made, the effects of thioridazine were studied at both therapeutic and toxic dose levels. The drug effects were first tested 15 minutes after intravenous injection of 10 mg/kg (therapeutic dose). An additional 40 mg/kg of thioridazine was then injected to bring the cumulative dose to 50 mg/kg (toxic dose), and the study was repeated 15 minutes after the additional injection. The dose of 10 mg/kg has been used to demonstrate antiarrhythmic effects of the drug by others, and it is well within the therapeutic daily dosage recommended for human beings.[1] In the initial four dogs, 10 mg/kg of thioridazine was administered every 15 minutes to permit observations of changes in idioventricular automaticity and arterial pressure. These variables were greatly decreased by the cumulative dose of 50 mg/kg, which was chosen as a toxic dose level.

Results

Figure 1 illustrates the effects of thioridazine on ventricular electrophysiologic properties studied in 12 dogs. Diastolic threshold, effective refractory period and conduction time were all increased after administration of 10 mg/kg (therapeutic dose) of thioridazine and they were further increased after the cumulative dose of 50 mg/kg (toxic dose) was administered in all animals. The mean diastolic threshold was 0.30 ± 0.04 milliamperes (ma) in the control period and increased to 0.60 ± 0.06 ma ($P < 0.001$) after 10 mg/kg and to 0.98 ± 0.11 ma ($P < 0.001$) after 50 mg/kg of thioridazine. The mean effective refractory period was 196 ± 4 msec in the control period and increased to 213 ± 3 msec ($P < 0.001$) after 10 mg/kg and to 230 ± 4 msec ($P < 0.001$) after 50 mg/kg. The mean conduction time was 46 ± 2 msec in the control period and increased to 51 ± 2 msec ($P < 0.01$) after 10 mg/kg and to 88 ± 4 msec ($P < 0.001$) after 50 mg/kg. The mean R-R interval of idioventricular rhythm was 880 ± 48 msec in the control period and increased to 1,049 ± 69 msec ($P < 0.001$) after 10 mg/kg and to 1,690 ± 101 msec ($P < 0.001$) after 50 mg/kg of the drug.

Figure 2 shows the results of a typical experiment demonstrating the decreased automaticity. The R-R interval was 940 msec in the control period and increased to 1,080 msec after 10 mg/kg and to 1,840 msec after 50 mg/kg of thioridazine.

Figure 3 depicts the results of a typical experiment showing increased vulnerability to ventricular arrhythmia at a toxic dose level of thioridazine. In this experiment, the ventricle was paced with basic stimuli (S_1) at a cycle length of 400 msec; after the 12th basic S_1, two premature stimuli (S_2 and S_3) were applied to produce two premature beats at the earliest possible intervals. No rapidly repetitive beats were induced by the introduction of two early premature beats either in the control period or after 10 mg/kg of thioridazine (panels A and B). However, rapidly repetitive beats developed immediately after the introduction of two early premature beats after 50 mg/kg of the drug (panel C). This occurred when ventricular conduction was severely depressed, as evidenced by greatly prolonged QRS complexes at the toxic dose level. The same experiment was carried out in 12 dogs. Repetitive beats did not occur in these dogs before or after 10 mg/kg of

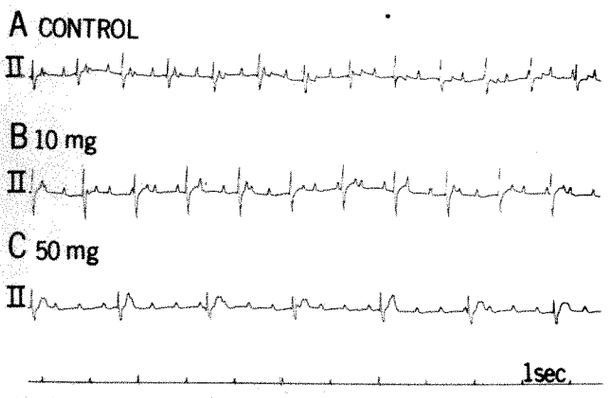


FIGURE 2. Effect of thioridazine on idioventricular rate. See text.

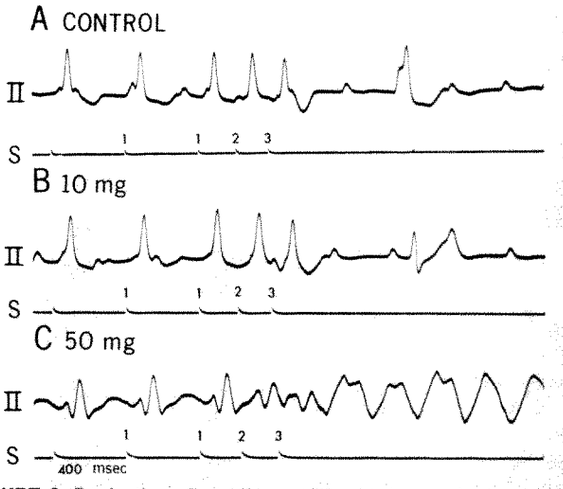


FIGURE 3. Production of rapidly repetitive responses by two early premature beats after administration of 50 mg/kg of thioridazine. See text for detailed description.

thioridazine but developed in nine dogs after the 50 mg/kg dose.

Discussion

Life-threatening cardiac complications of phenothiazines or tricyclic antidepressant agents have been observed clinically by several investigators.[5–9] Kelly et al.[5] reported that two patients died of cardiac arrhythmias while receiving thioridazine in a daily dose of 1,500 and 3,600 mg, respectively. Ventricular arrhythmias have been thought to be the major cause of death associated with phenothiazines. However, antiarrhythmic properties of phenothiazines have also been documented in animal experiments.[1–4] These apparent parodoxical effects of phenothiazines have not been clearly explained. Our results indicate that the antiarrhythmic and arrhythmogenic effects are dose-dependent. We confirmed the quinidine-like action of thioridazine when it was administered in a therapeutic dose (10 mg/kg) but found that the drug increased ventricular vulnerability to arrhythmia when given in a toxic dose (50 mg/kg).

In our study, diastolic threshold, effective refractory period and conduction time were significantly increased and idioventricular antomaticity was suppressed by a therapeutic dose of thioridazine. Antiarrhythmic properties of the drug can be attributed to the observed increase in diastolic threshold and effective refractory period and the decrease in automaticity. Thioridazine in a toxic dose further increased diastolic threshold, effective refractory period and conduction time and further suppressed idioventricular automaticity. Rapidly repetitive responses or tachycardia could be induced in the ventricle by two early premature beats in 9 of 12 dogs after a toxic dose of thioridazine, but they did not occur before or after a therapeutic dose of the drug. Our earlier studies[10,11] indicated that the repetitive responses induced by early premature beats are most likely due to the mechanism of reentry. Greatly slowed conduction is expected to favor the development of reentrant activity in the ventricle.[12]

Clinical implications: The deleterious effects of toxic doses of thioridazine could also be due to greatly suppressed idioventricular automaticity. The drug is also expected to suppress other automatic fibers and to produce cardiac asystole. Because the inhibition of centrally mediated pressor reflexes and the alpha adrenergic blocking effects of thioridazine are well known,[13] a significant decrease in blood pressure is also expected to occur. A marked decrease in ventricular rate and blood pressure would lead to a low cardiac output state and even to death. Our study indicates that caution should be exercised in patients receiving large doses of phenothiazine derivatives, and electrocardiograms and blood pressure should be frequently monitored in these patients.

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Multiple Gated Cardiac Blood Pool Imaging for Left Ventricular Ejection Fraction: Validation of the Technique and Assessment of Variability

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The intrinsic variability and accuracy of left ventricular ejection fraction determined by multiple gated cardiac blood pool imaging was evaluated in 83 patients. Ejection fraction by gated studies correlated well with data from first pass radionuclide angiocardiography ($r = 0.94$) and from contrast angiography ($r = 0.84$). Intra- and interobserver variabilities of absolute ejection fraction were minimal (mean ± standard deviation 1.4 ± 1.2 and 1.6 ± 1.5 percent, respectively) and were not different for normal (ejection fraction 55 percent or greater) and abnormal patients. Ejection fraction was determined twice in 70 patients: on the same day at intervals separated by 1 to 2 hours (41 patients) and on 2 different days (29 patients). Ejection fraction ranged from 18 to 91 percent and was normal in 37 patients. There was no difference in mean serial variabilities of absolute ejection fraction for all repeat studies performed on the same and separate days (3.3 ± 3.1 versus 4.3 ± 3.1 percent (not significantly different). The mean variability of absolute ejection fraction for repeat studies in normal patients was significantly greater than in abnormal patients (5.4 ± 4.4 versus 2.1 ± 2.0 percent, $P < 0.01$). The incidence rate of absolute interstudy changes of 5 percent or more was significantly higher in normal than in abnormal patients ($P < 0.01$). This differential variability should be considered in interpreting sequential changes in left ventricular ejection fraction. To be attributed to nonrandom physiologic alterations, the absolute change in ejection fraction should be 10 percent or more in normal patients and 5 percent or more in abnormal patients.

Since its introduction in 1971,[1] electrocardiographically gated cardiac blood pool imaging has gained widespread clinical acceptance for the noninvasive assessment of left ventricular function. The recent development of computer techniques[2–5] that allow for simultaneous acquisition of data from multiple parts of each cardiac cycle (multiple gated cardiac blood pool imaging) has added precision to analysis and has further broadened application. The ability to obtain serial measurement of left ventricular ejection fraction after a single isotope injection makes this technique of monitoring left ventricular function particularly appealing. Recent studies[6–10] have indicated excellent correlations between data derived from multiple gated imaging and contrast angiography. However, before multiple gated imaging can be used meaningfully to follow up patients in a sequential manner, the intrinsic variability of this technique must be defined. The reproducibility and intrinsic variability of multiple gated imaging determined in a large series of patients have not been described. Furthermore, it is not known whether these deter-

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minations are comparable over the range of values for left ventricular ejection fraction encountered in both normal and abnormal subjects.

The purpose of this study was to evaluate the reproducibility and intrinsic variability of serial determinations of left ventricular ejection fraction obtained by multiple gated imaging. In addition, data obtained with this technique were compared with those derived from contrast left ventricular angiography and first pass radionuclide angiocardiography using a computerized multicrystal scintillation camera.

Methods

Case Material

Patient selection: Eighty-three randomly selected patients referred for radionuclide assessment of left ventricular function were included in this study. Sixty patients had coronary artery disease, 4 mitral regurgitation, 2 mitral stenosis, 2 aortic regurgitation, 4 aortic stenosis and 11 miscellaneous conditions. No patient had acute myocardial infarction or unstable angina. At the time of study, all had normal sinus rhythm. A total of one hundred seventy-three individual multiple gated studies were obtained. Sixty-four patients had both multiple gated imaging and first pass radionuclide angiocardiography, and 26 of these also underwent contrast angiography. Interstudy comparisons then were made.

Intra- and interobserver variability: Intraobserver variability was determined in 156 randomly selected multiple gated studies processed twice by the same operator (F.W.). Analyses were separated by 5 to 21 days, and were performed without knowledge of the original result. Interobserver variability was determined independently in 38 multiple gated studies that were processed again by a second observer (D.J.), who at that time had minimal experience with the technique.

Variability on the same day and on different days: In 41 randomly selected patients, two multiple gated studies were performed on 1 day, 1 to 2 hours apart. Between the two studies the patients were free to move about and thus had to be repositioned beneath the scintillation camera for the second study. In 29 randomly selected patients, multiple gated studies were performed on 2 different days, 1 to 5 days apart. All patients were in clinically stable condition within this time period. In both groups, all studies were reprocessed by a single observer (F.W.) to evaluate intraobserver variability; these data also are included in the overall analysis described earlier.

Comparison of ejection fraction by multiple gated imaging and first pass radionuclide angiocardiography: In 64 randomly selected patients, left ventricular ejection fraction was determined initially by first pass radionuclide angiocardiography and within 45 minutes by multiple gated imaging. The first pass study was obtained with a bolus injection of technetium-99m pertechnetate. This same bolus dose of technetium-99m then was used for in vivo red blood cell labeling in the subsequent gated study (see later).

Comparison of ejection fraction by radionuclide techniques and contrast angiography: In 26 patients within the study group, contrast angiography was performed within 2 days of the radionuclide studies. All patients were in clinically stable condition within this time period.

Data Analysis

All data processing of individual studies was performed without knowledge of the other radionuclide, contrast angiographic and clinical data.

Radionuclide techniques: *Multiple gated imaging:* A mobile single crystal scintillation camera equipped with a high sensitivity parallel hole collimator (Picker Dynamo, Northford, Connecticut) and a commercially available portable computer system(MUGA Cart, Medical Data Systems, Ann Arbor, Michigan) were used. For all studies, imaging was performed with the in vivo labeled red blood cell technique.[11–13] This was accomplished, as previously described, by intravenous injection of 15 mg of cold stannous pyrophosphate dissolved in 3 ml of normal saline solution followed 15 to 30 minutes later by administration of 25 mCi of technetium-99m pertechnetate. The 20 percent energy window was peaked symmetrically around 140 kev. All multiple gated studies were acquired with the patient supine and the detector head in 45° left anterior oblique position and caudal tilt. Care was taken to adjust the position of the detector to separate clearly the right and left ventricles. Scintillation data were accumulated in list mode and stored in histogram form (32 by 32 word mode, interpolated to 64 by 64 word mode) in a computer core memory using the R wave of the electrocardiogram as the synchronizing impulse. The cardiac cycle was divided into 28 equal frames. For each frame, 150,000 to 200,000 counts were accumulated in the whole field of view, resulting in 6,000 to 8,000 counts in the left ventricle at end-diastole. The average acquisition time for a gated study was approximately 6 minutes.

Processing was performed using a commercially available computer program (Medical Data Systems, SUP8-MUGE) and required approximately 4 minutes. The 28 frames were displayed as an endless loop movie on the oscilloscope in order to determine visually the outline of the left ventricle. The left ventricular region of interest was determined by placing a rectangle outside the borders of the left ventricle in end-diastole. Edge detection of the left ventricular blood pool was obtained by determination of the second derivative of counts starting from the center of maximal activity within the region of interest. Data were not smoothed or averaged. The criteria for left ventricular edge detection were determined by the operator in the first (end-diastolic) frame. Care was taken that the edges of the region of interest agreed with the anatomic outline of the left ventricle as seen in the movie display. Any portion of the region that involved the aorta or left atrium was excluded. After setting of the criteria for edge detection in the first frame, a new region of interest was determined for each of the subsequent 27 frames. Using the semiautomated computer mode, the operator verified and corrected as necessary each frame. Background activity was determined automatically as a posterolateral 90° crescent five channels wide and separated from the end-systolic edge by five channels. The average counts per channel in the background region of interest was subtracted from each channel in the variable left ventricular region of interest.

A background-corrected time-acitivity curve was displayed automatically with the computer value for left ventricular ejection fraction. If the curve approached that of an ideal ventricular volume curve, the study was considered adequate. If not, processing was repeated. Left ventricular ejection fraction is derived from the equation: end-diastolic counts minus end-systolic counts divided by end-diastolic counts, times 100.

First pass radionuclide angiocardiography: In the patients who had both radionuclide studies, the first pass study was always performed before the multiple gated study. A computerized multicrystal scintillation camera (Baird-Atomic System 77, Bedford, Massachusetts) was used for the first pass studies. This method previously has been standardized and validated in this laboratory.[14–16] In brief, studies are per-

formed with the patient supine and the detector head of the camera in the anterior position. Twenty-five mCi of technetium-99m pertechnetate, used subsequently for in vivo labeling of red blood cells, was injected rapidly as a bolus dose through an intravenous catheter in an antecubital vein. A high frequency background-corrected radionuclide time-activity curve was generated over a left ventricular region of interest, from which left ventricular ejection fraction was calculated. The processing time by an experienced operator to obtain left ventricular ejection fraction from the first pass study averaged less than 10 minutes.

Contrast angiography: Left ventricular volumes were determined from 30° right anterior oblique angiograms. Only those ventriculograms free of ectopy were considered technically satisfactory. The end-diastolic and end-systolic frames, including papillary muscles and trabeculations, were traced. The coordinates of these outlines were digitized (Numonics Digitizer, Numonics Corp., Lansdale, Pennsylvania), and volumes were calculated by direct integration[17] using a Varian 6201 Minicomputer (Varian, Irvine, California). This method divides the left ventricle into 1 mm thick cylindrical slices, without correction for rotation or distortion. Total left ventricular volume is obtained by summing the volumes of each segment, and left ventricular ejection fraction is derived according to the conventional formula.

Statistical analysis: Data are presented as the mean ± standard deviation. A left ventricular ejection fraction of 55 percent or more was considered normal. Variability was defined as the absolute difference between two determinations of left ventricular ejection fraction from the same data acquisition or from two separate studies. Variabilities among groups were compared with Student's t test. Data in individual patients were analyzed with the paired t test. The significance of differences in incidence was tested by the chi square test. A probability (P) value of <0.05 was considered significant.

Results

Intra- and interobserver variability (Fig. 1): The mean intraobserver variability of absolute ejection fraction determined from reprocessing 156 gated studies was 1.4 ± 1.2 percent (range 0 to 5 percent). There was no difference in values for intraobserver variability in the 78 patients with a normal ejection fraction and the 78 with an abnormal ejection fraction (1.3 ± 0.9 versus 1.5 ± 1.4 percent, respectively, P = not significant [NS]). The mean interobserver variability determined from reprocessing 38 gated studies was 1.6 ± 1.5 percent (range of 0 to 6 percent). There was no difference in the interobserver variability values of patients with normal and abnormal ejection fraction (1.9 ± 1.3 versus 1.3 ± 1.7 percent, respectively, P = NS). In addition, inter- and intraobserver variability values of absolute ejection fraction were not significantly different (Fig. 2).

Variability on the same day and on different days (Fig. 3): The mean serial variability of absolute ejection fraction in repeat gated studies on the same day in 41 patients was 3.3 ± 3.1 percent. Ejection fraction averaged 53.3 ± 20.4 for the initial study and 53.8 ± 19.9 percent for the repeat study (P = NS). Initial and repeat determinations of ejection fraction had an excellent correlation (r = 0.97). The heart rates at the time of initial and repeat studies were not significantly different (73 ± 15 versus 74 ± 15 beats/min, P = NS). Ejection fraction ranged from 18 to 91 percent. Nineteen patients had an abnormal and 22 had a normal ejection fraction as determined with the initial gated study. The mean serial variability for normal patients was significantly larger than for abnormal patients (4.6 ± 4.7 versus 2.0 ± 1.6 percent, respectively, P <0.05) (Fig. 2). In addition, the mean serial variability for normal patients was significantly larger than the intraobserver variability (P <0.01) in this group.

The mean serial variability of absolute ejection fraction in repeat gated studies in the group of 29 patients studied on different days was 4.3 ± 3.1 percent. Ejection fraction averaged 53.9 ± 17.6 percent for the initial study and 53.3 ± 16.9 percent for the repeat studies (P = NS). Initial and repeat values of ejection fraction had an excellent correlation (r = 0.93). The heart rates at the times of initial and repeat studies were not significantly different (71 ± 17 versus 71 ± 16

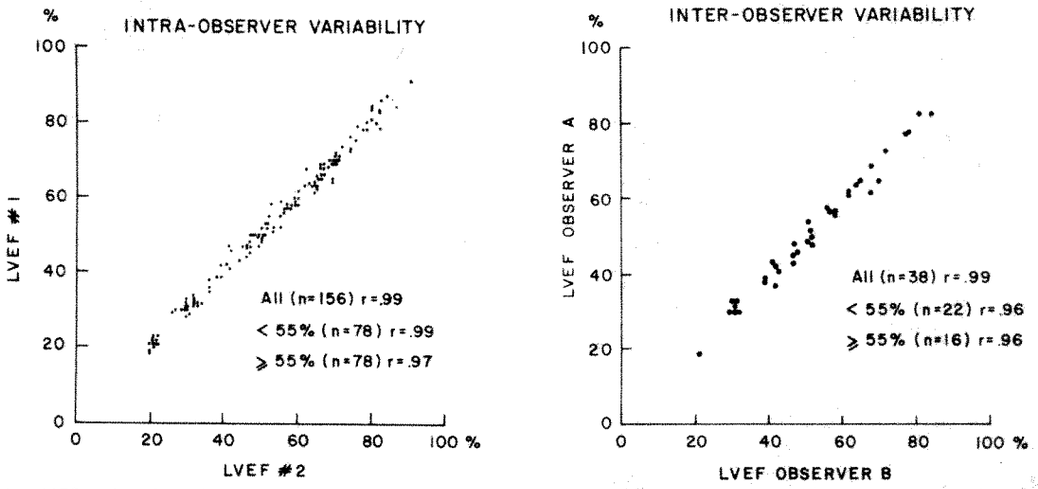


FIGURE 1. Intra- (156 patients) and interobserver (38 patients) variability in determination of left ventricular ejection fraction (LVEF) with multiple gated imaging. Note the excellent correlation (r values) in both the normal (ejection fraction 55 percent or more) and abnormal (ejection fraction less than 55 percent) subjects. n = number of patients.

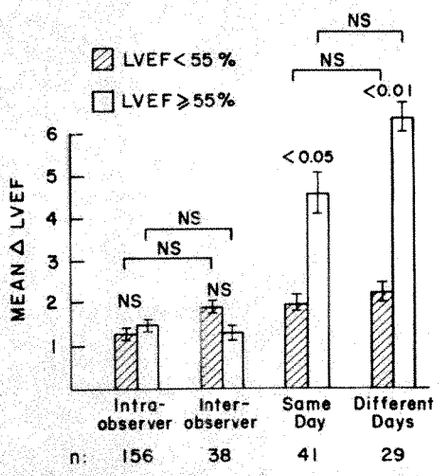


FIGURE 2. Mean variability (Δ) of left ventricular ejection fraction (LVEF) assessed from multiple gated imaging by reprocessing the data by the same (intraobserver) or different observers (interobserver) and by repeat studies on the same or different days. The mean variability of patients with an abnormal ejection fraction (less than 55 percent) is compared with that in patients with a normal ejection fraction (55 percent or more). There is no significant difference in intra- and interobserver variability in abnormal with normal patients. A significant difference exists between mean variability in ejection fraction on repeat studies in subjects with a normal or abnormal ejection fraction whether they were studied on the same or different days. Within each group (that is, normal or abnormal) there is no difference in mean variability in ejection fraction whether studies were performed on the same or different days. n = number of patients; NS = not significant.

TABLE I

Variability of Left Ventricular Ejection Fraction Assessed With Repeat Multiple Gated Imaging on the Same Day in 41 Patients

LVEF <55%				LVEF ≥55%			
Case no.	Study 1	Study 2	Δ LVEF	Case no.	Study 1	Study 2	Δ LVEF
1	22	21	1	20	70	69	1
2	53	58	5	21	75	84	9
3	38	39	1	22	60	81	21
4	50	52	2	23	66	71	5
5	50	45	5	24	87	79	8
6	50	48	2	25	68	63	5
7	20	22	2	26	83	80	3
8	32	30	2	27	69	72	3
9	32	32	0	28	71	68	3
10	34	35	1	29	78	78	0
11	31	33	2	30	72	69	3
12	49	53	4	31	65	68	3
13	50	50	0	32	91	83	8
14	50	50	0	33	73	70	3
15	21	19	2	34	72	66	6
16	18	23	5	35	60	58	2
17	21	23	2	36	59	60	1
18	22	21	1	37	65	63	2
19	28	29	1	38	59	47	12
				39	57	55	2
				40	57	58	1
				41	70	69	1
Mean Values ± Standard Deviation							
	35.3 ± 12.8	35.9 ± 12.9	2 ± 1.6		68.8 ± 10.3	69.2 ± 8.6	4.6 ± 4.7

LVEF = left ventricular ejection fraction (%); Δ = absolute change.

beats/min, P = NS). Ejection fraction ranged from 18 to 83 percent. Fourteen patients had an abnormal and 15 had a normal ejection fraction as determined in the initial gated study. The mean serial variability of absolute ejection fraction in those with a normal ejection fraction was significantly larger than in those with an abnormal value (6.4 ± 3.7 versus 2.3 ± 2.5 percent, respectively, $P < .01$) (Fig. 2). In addition, the mean serial variability for patients with a normal ejection fraction also was significantly larger than the intraobserver variability ($P < 0.01$). There was no significant difference between the values for serial variability on the same day and on different days. The mean serial vari-

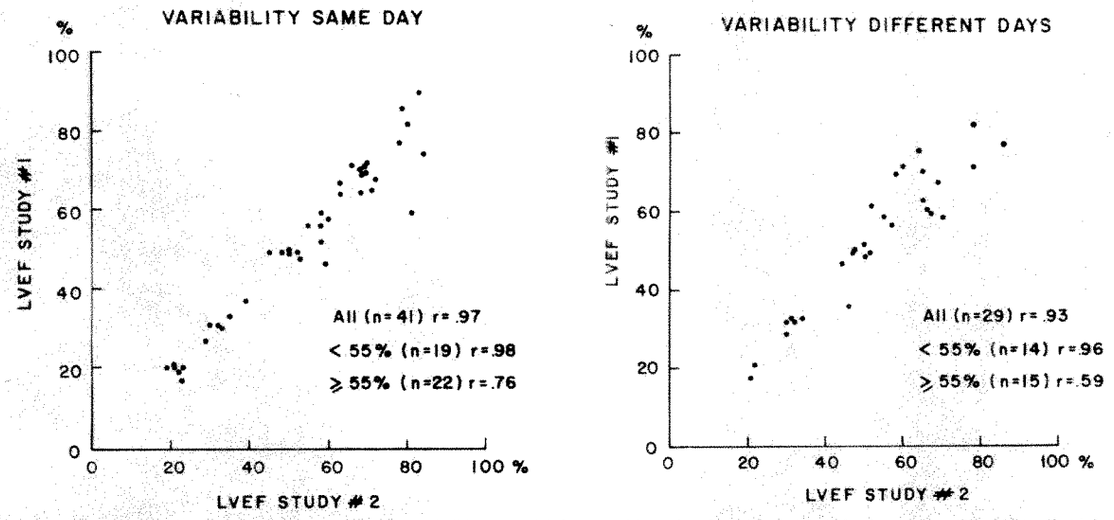


FIGURE 3. Variability of left ventricular ejection fraction (LVEF) by multiple gated imaging in the same patient on the same (41 patients) or different (29 patients) days. The correlations (r values) are less impressive in patients with a normal ejection fraction (55 percent or more). n = number of patients.

TABLE II

Variability of Left Ventricular Ejection Fraction Assessed With Repeat Multiple Gated Imaging on Different Days in 39 Patients

LVEF <55%				LVEF ≥55%			
Case no.	Study 1	Study 2	Δ LVEF	Case no.	Study 1	Study 2	Δ LVEF
1	32	32	0	15	62	52	10
2	50	51	1	16	68	69	1
3	52	50	2	17	71	65	6
4	36	46	10	18	83	78	5
5	33	31	2	19	61	66	5
6	50	47	3	20	78	86	8
7	33	34	1	21	63	65	2
8	49	50	1	22	76	64	12
9	50	47	3	23	60	67	7
10	29	30	1	24	59	55	4
11	47	44	3	25	70	58	12
12	21	22	1	26	72	78	6
13	18	21	3	27	72	64	8
14	32	30	2	28	59	70	11
				29	57	57	0
Mean Values ± Standard Deviation							
	38.4 ± 11.8	38.8 ± 10.8	2.3 ± 2.5		67.4 ± 7.9	66.0 ± 9.3	6.4 ± 3.7

LVEF = left ventricular ejection fraction (%); Δ = absolute change.

TABLE III

Incidence of Various Degrees of Interstudy Variability in Absolute Left Ventricular Ejection Fraction Assessed With Repeat Multiple Gated Imaging in 70 Patients

LVEF < 55%				LVEF ≥ 55%			
		Cumulative				Cumulative	
Δ LVEF (%)	no. of Pts	no. of Pts	% Pts	Δ LVEF (%)	no. of Pts	no. of Pts	% Pts
10	1	1	3%	21	1	1	3%
5	3	4	12%	12	3	4	11%
4	1	5	15%	11	1	5	14%
3	4	9	27%	10	1	6	16%
2	10	19	58%	9	1	7	19%
1	10	29	88%	8	4	11	30%
0	4	33	100%	7	1	12	32%
				6	3	15	41%
				5	4	19	51%
				4	1	20	54%
				3	6	26	70%
				2	4	30	81%
				1	5	35	95%
				0	2	37	100%

LVEF = left ventricular ejection fraction; Pts = patients; Δ = absolute change.

ability of all repeat studies, on either the same or different days, was 3.9 ± 3.1 percent for the overall group of 70 patients. The mean serial variability of absolute ejection fraction was 2.1 ± 2.0 percent for the 33 with an abnormal ejection fraction and 5.4 ± 4.4 percent for the 37 with a normal ejection fraction ($P < 0.01$).

Of the patients studied twice on the same day, two had an abnormal ejection fraction (47 and 53 percent, respectively) in one study and a normal ejection fraction (59 and 58 percent) in the other (Table I). Of the patients studied on different days, one had a normal ejection fraction (62 percent) in the initial study and an abnormal ejection fraction (52 percent) in the repeat study (Table II).

The cumulative incidence of various degrees of interstudy variability of absolute ejection fraction is shown in Table III. At least 5 percent absolute variability occurred in 23 of the 70 patients. This degree of variability was noted in 4 of the 33 patients (12 percent) with an abnormal ejection fraction and in 19 of the 37 (51 percent) with a normal ejection fraction. The incidence of at least 5 percent absolute variability was significantly greater in patients with a normal than in those with an abnormal ejection fraction ($P < 0.01$). Ten percent or more absolute variability occurred in seven patients, one (3 percent) with an abnormal ejection fraction and six (16 percent) with a normal ejection fraction. There was no difference in the incidence of at least 10 percent absolute variability (P = not significant). Thus, a minimal absolute change of 10 percent for normal patients and of 5 percent for abnormal patients is not likely to be attributed to random physiologic alterations.

Comparison of ejection fraction assessed with multiple gated imaging and first pass angiocardiography (Fig. 4): In the 64 patients studied with these procedures, ejection fraction averaged 52.5 ± 17.5 percent on gated imaging and 50.2 ± 18.7 percent on first pass study ($P < 0.01$). Ejection fractions determined with these two radionuclide techniques had an excellent correlation ($r = 0.94$) over the entire range of ejection fractions (18 to 91 percent). In the 30 patients with an abnormal ejection fraction on first pass study the values obtained with gated studies were consistently higher than the values obtained with first pass angiocardiography (37.3 ± 11.6 versus 33.1 ± 11 percent, respectively, $P < 0.01$). However, in the 34 patients with a normal ejection fraction, there was no difference between values obtained with the gated and first pass studies (65.9 ± 8.4 versus 65.3 ± 7.9 percent, respectively, P = not significant).

Comparison of ejection fraction assessed with radionuclide techniques and contrast angiocardiography (Fig. 5): There was a good correlation between ejection fraction derived from contrast angiocardiography and from either multiple gated studies ($r = 0.84$) or first pass angiocardiography ($r = 0.89$). In 26 patients studied with the three techniques the mean ejection fraction was 57.9 ± 15.9 percent on gated imaging, 56.3 ± 17.0 percent on first pass angiocardiography and 59.0 ± 16.9 percent on contrast angiography. There was no significant difference among these three mean values. Of the 26 patients included in this part of the study, 9 had on abnormal ejection fraction as determined with contrast angiocardiography. One patient with an abnormal ejection fraction (49 percent) on contrast angiocardiography had a normal ejection fraction (57 percent) on gated study. Among the patients with an abnormal ejection fraction there was no disagreement between first pass and contrast angio-

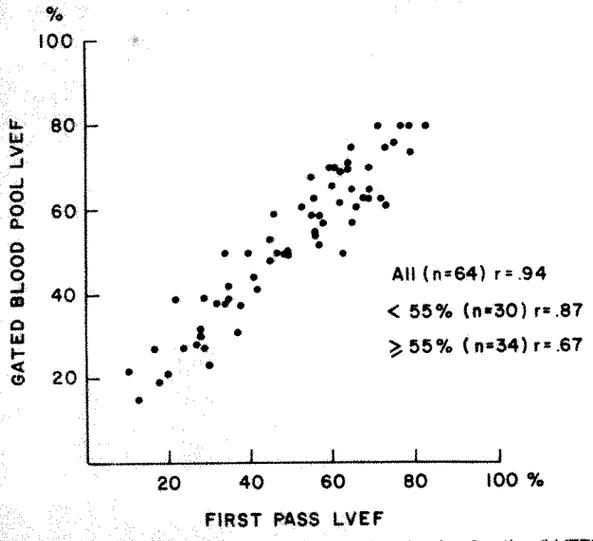


FIGURE 4. Correlation between left ventricular ejection fraction (LVEF) assessed with multiple gated blood pool imaging and first pass radionuclide angiocardiography in 64 patients. The correlation (r value) is not as good in patients with a normal ejection fraction (55 percent or more). n = number of patients.

cardiographic findings. Two patients with a normal ejection fraction (both 55 percent) on contrast angiocardiography had an abnormal ejection fraction in the gated studies (both 40 percent) and on first pass (47 and 40 percent, respectively). There was no significant difference among the mean values for ejection fraction of those with either an abnormal or a normal ejection fraction determined with the two radionuclide techniques and contrast angiography.

Discussion

Our study demonstrates that left ventricular ejection fraction determined with multiple gated blood pool imaging is a highly accurate and reproducible index of left ventricular performance that correlates with measurements made with left ventricular contrast angiography. In addition, measurements of left ventricular ejection fraction using multiple gated imaging and first-pass radionuclide angiocardiography also correlate closely. In both techniques, ejection fraction is calculated from changes in radioactivity that are assumed to be proportional to changes in ventricular volume. Thus the determination of left ventricular ejection fraction is free of the geometrical assumptions inherent in conventional volume calculations using contrast angiocardiography. Reproducible sequential studies can be performed with both radionuclide techniques. However, multiple gated imaging allows repeated measurements of ejection fraction over several hours from a single radioisotope injection. Data processing of indiviudal studies is comparable for the two techniques, but data acquisition is markedly shorter for first pass studies.

Difference in variability between patients with a normal and abnormal ejection fraction: This study also demonstrates that the intrinsic variability of absolute ejection fraction in serial measurements of left ventricular ejection fraction appears to be related to the baseline level of ventricular function. Absolute variability is significantly greater in patients with a normal than in those with an abnormal ejection fraction. This differential variability is not due to errors in data processing, because intra- and interobserver variabilities are minimal and not different in patients with normal and abnormal ejection fractions. In addition, although technical factors, such as defining background zones and regions of interest, have been shown to affect normal more than abnormal ejection fractions,[18] such errors would be systematic and should not necessarily affect interstudy variability.

The difference in variability between patients with a normal and abnormal ejection fraction may be a re-

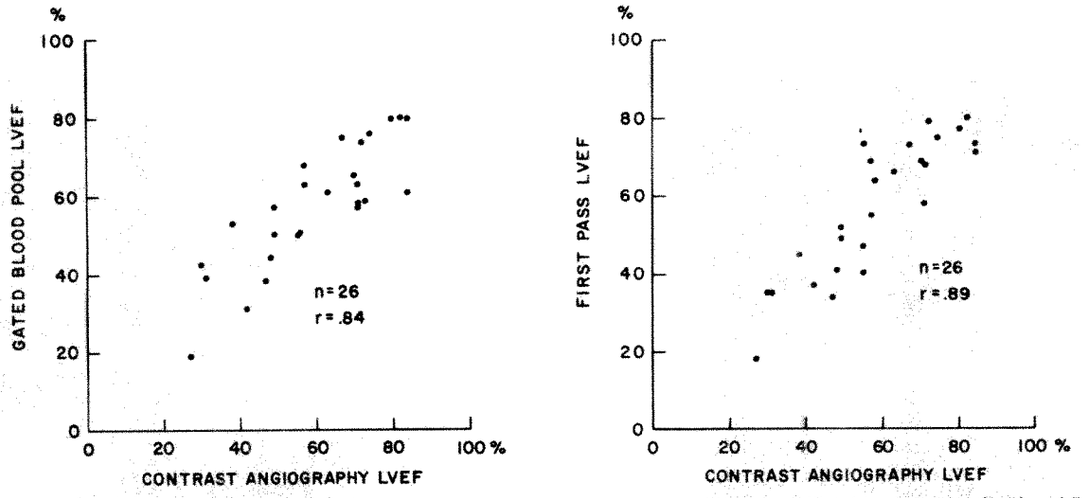


FIGURE 5. Correlation between left ventricular ejection fraction (LVEF) assessed with multiple gated blood pool imaging **(left)** and first pass radionuclide angiocardiography **(right)** with ejection fraction determined with left ventricular contrast angiography in 26 patients.

flection of a pathophysiologic phenomenon. In patients with normal left ventricular performance there is greater ventricular reserve and hence a greater chance of responding to a variety of stimuli with augmentation of cardiac pump function. In patients with abnormal basal ventricular performance such as those with an ejection fraction of 20 to 30 percent, the ventricle is presumably already working at close to maximal effort and will therefore have less tendency to manifest comparable spontaneous fluctuations in a ventricular pump performance index such as ejection fraction. If the data are analyzed in terms of relative percent changes rather than absolute changes (for example, a change in ejection fraction from 50 to 45 percent would represent a relative change of 10 percent and an absolute change of 5 percent), then there is no significant difference between patients with a normal and an abnormal ejection fraction (8.0 ± 7.2 versus 6.6 ± 6.3 percent, respectively). Thus, although variability of ejection fraction in absolute numbers is greater in patients with a normal ejection fraction, the variability in relative terms is comparable between the two groups.

The absolute variability of serial measurements of ejection fraction determined with the first pass radionuclide technique used in this study was recently reported from this laboratory.[15] Although the overall variability was 4.4 ± 3.6 percent, a value comparable with that of multiple gated imaging, there was no difference between data in the normal and abnormal groups. The reason for this difference between the two radionuclide techniques is not clear, but it may reflect patient selection or methodologic differences.

Variability of repeat measurements by multiple gated imaging: Previous studies[6–8] demonstrated that left ventricular ejection fraction can be determined accurately from multiple gated imaging, with acceptable levels of inter- and intraobserver variability. These findings were confirmed in our present study. However, limited data are available on the variability of repeat measurements of ejection fraction obtained with multiple gated imaging. Maddahi et al.[10] noted in preliminary reports a mean variability of 5.7 ± 4.8 percent for two determinations of ejection fraction separated by 30 minutes. Folland et al.[7] described unpublished data demonstrating that 95 percent of repeat measurements separated by 30 minutes differed by less than 6 percent. Neither group commented on differences between patients with a normal and an abnormal ejection fraction and neither studied patients on two separate days.

Our data demonstrated that interstudy variability was indistinguishable whether the studies were performed on the same or on different days. When the studies were performed on the same day, the patients' activity was not restricted between studies. In each case the patient and camera had to be completely repositioned. This condition closely approximates the situation encountered when an ambulatory patient or a hospitalized patient in the coronary care unit is studied sequentially on the same day.

Clinical implications: Establishment of the intrinsic variability of serial measurements of left ventricular ejection fraction obtained using multiple gated imaging has relevant clinical and investigative implications. Because at least 5 percent absolute variability occurred in only 12 percent of patients with an abnormal ejection fraction but in 51 percent of those with a normal ejection fraction, it is clear that different levels of confidence need to be considered in patients with normal and abnormal baseline ventricular performance. The data demonstrate that an absolute change of 5 percent in ejection fraction is more likely to represent a nonrandom rather than a random difference in a patient with an abnormal ejection fraction as opposed to one with a normal ejection fraction. In practical terms, we selected absolute changes of at least 10 percent in patients with a normal ejection fraction and of at least 5 percent in patients with an abnormal ejection fraction as limits for assessing significant serial alterations in left ventricular ejection fraction in individual patients. Smaller changes may be significant in immoblized patients. In addition, consistent trends of smaller magnitude in large groups of patients also may prove significant.

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Clinical Evaluation of Automated Processing of Electrocardiograms By the Veterans Administration Program (AVA 3.4)

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Automated processing of electrocardiograms by the Veterans Administration program was evaluated for both agreement with physician interpretation and interpretative accuracy as assessed with nonelectrocardiographic criteria. One thousand unselected electrocardiograms were analyzed by two reviewer groups, one familiar and the other unfamiliar with the computer program. A significant number of measurement errors involving repolarization changes and left axis deviation occurred; however, interpretative disagreements related to statistical decision were largely language-related. Use of a printout with a more traditional format resulted in agreement with physician interpretation by both reviewer groups in more than 80 percent of cases. Overall sensitivity based on agreement with nonelectrocardiographic criteria was significantly greater with use of the computer program than with use of the conventional criteria utilized by the reviewers. This difference was particularly evident in the subgroup analysis of myocardial infarction and left ventricular hypertrophy. The degree of overdiagnosis of left ventricular hypertrophy and posteroinferior infarction was initially unacceptable, but this difficulty was corrected by adjustment of probabilities. Clinical acceptability of the Veterans Administration program appears to require greater physician education than that needed for other computer programs of electrocardiographic analysis; the flexibility of interpretation by statistical decision offers the potential for better diagnostic accuracy.

Most programs available for automated processing of electrocardiograms utilize an analytic approach that attempts to simulate the conventional interpretative technique of the physician.[1-8] Evaluation of these programs has primarily emphasized agreement with physician interpretation because the performance of a clinically acceptable system should be comparable with that of the physician.[2] However, the benefit of this approach to automated electrocardiographic analysis is mainly that of improvement in physician time efficiency because the accuracy in interpretation remains no better than that available with use of conventional criteria. The limited diagnostic accuracy of conventional electrocardiographic criteria is well recognized,[10] and to achieve significant improvement may require a different approach to analysis of electrocardiographic information. One such approach is that of Pipberger and associates,[11,12] whose computer system classifies electrocardiograms diagnostically on the basis of statistical decision-making. Because this system uses an interpretative method unrelated to the traditional approach, an objective evaluation of its accuracy must be based on a reference standard other than that of conventional electrocardiographic criteria. Recently Pipberger et al.[13] reported the results of a study of diagnostic accuracy and noted a significant improvement over accuracy achieved with conventional analysis. Inherent in this improvement, however, is the potential for increased disagreement between physician

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and computer diagnosis which if too great may affect physician acceptability of automated analysis. In this report we evaluate the Veterans Administration program in an independent clinical setting and consider the problems encountered in its clinical applicability.

Methods

Computer program: The Veterans Administration program (version AVA 3.4), previously implemented on a CDC 3300 computer at the Minneapolis Veterans Administration Hospital, has been in operation since December 1973. Details of its development, structure and mode of operation have been described.[14–16] Briefly, after determination of rhythm, an initial heuristic approach directs the analysis to four diagnostic groups. Within each of these groups an unknown record is classified among several diagnostic categories by means of a likelihood ratio test using Bayesian approach developed by Cornfield.[17] Table I shows the various diagnostic categories considered in the classification process. Estimated "prior probabilities" are inserted in the algorithm and represent the prevalence of various electrocardiographic categories in the different clinical groups of the population studied.* Each condition reported by the program after the electrocardiographic analysis is then accompanied by a relative posterior probability value.

Electrocardiograms to be processed by the computer program were recorded on a Hewlett-Packard electrocardiographic cart, model 1516A. Although both the standard 12 lead and XYZ lead recordings were obtained as a paper tracing, only the XYZ leads were recorded on magnetic tape. Patient identification and prior probability codes were entered immediately before XYZ lead recording by the technician from the information available in the patient's clinical record. The numerical values utilized in this study for the prior probability codes were those developed at the Veterans Administration Hospital in Washington, D.C.

Evaluation procedure: A total of 1,000 successive electrocardiograms obtained from an unselected group of ambulatory inpatients at the Minneapolis Veterans Administration Hospital were evaluated for two factors: (1) physician/computer agreement, and (2) physician versus computer diagnostic accuracy as judged by agreement with independent nonelectrocardiographic clinical data. For evaluation of physician/computer agreement, a two-step procedure was utilized. In step 1, six staff physicians involved in daily electrocardiographic reading reviewed the standard 12 lead tracing using criteria with which they were most familiar and recorded an interpretation before comparing their conclusions with those of the computer printout. In step 2, the same method of analysis was utilized by two staff cardiologists who were familiar with the Veterans Administration program and the Frank lead electrocardiogram. These physicians utilized criteria encompassed by the Minnesota code[18] for analyzing the standard 12 leads and also utilized the XYZ orthogonal lead tracing in arriving at their final interpretation. Initially, physicians in the step 1 study had difficulty in accepting the standard program printout, apparently because of lack of familiarity with XYZ lead measurements and criteria. The concept of probability interpretation also presented some difficulty when more than one principal abnormality was in question. Rather than attempt an in-depth evaluation of the problems associated with the format of the standard printout, we developed an additional printout that was more traditional in character (Fig. 1).

To analyze diagnostic accuracy using data independent from the electrocardiogram, we selected 507 tracings in which we thought the clinical diagnosis could be reliably related to the disease code categories in the Veterans Administration program. These clinical data were gathered from the patients' history, laboratory findings, X-ray film and angiographic studies and direct visualization of cardiac lesions at operation. The criteria for defining the various clinical disease code categories are noted in Table II. Because most of the patients were categorized as having either myocardial infarction, left ventricular hypertrophy, pulmonary disease or no cardiovascular disease, subgroup assessment was undertaken only for these categories. In this part of the study no attempt was made to analyze the myocardial infarction data in terms of localization of the lesion. Accuracy score data for the computer program and for the physician reviewer were based on the following (Fig. 2): For the computer program a printout probability value of 30 percent or greater for any primary diagnosis was considered significant. For the physician a written acknowledgment that a given abnormality was present or not was noted as well as a statement as to whether the diagnosis was possible, probable or definite.

The degree of agreement between the two methods of interpretation was assessed as (1) *complete agreement,* that is, the same diagnosis; (2) *minor disagreement,* which allowed for a difference in minor rhythm disturbance such as occasional premature ventricular or supraventricular complexes or minor ST-T wave discrepancies, or a difference of no more than one probability category of the primary diagnosis; and

TABLE I

Diagnostic Categories Reported by the Veterans Administration Program

Main QRS Analysis
1. Normal
2. Left ventricular hypertrophy
3. Right ventricular hypertrophy
4. Biventricular hypertrophy
5. Anterior wall myocardial infarction
6. Lateral wall myocardial infarction
7. Posteroinferior wall myocardial infarction
8. Chronic pulmonary disease

Conduction Defects
1. Left ventricular conduction defect
2. Left ventricular conduction defect with myocardial infarction
3. Right ventricular conduction defect
4. Right ventricular conduction defect with myocardial infarction

P Wave Analysis
1. Normal
2. Left atrial overload
3. Right atrial overload

ST-T Wave Analysis
1. Nonspecific ST-T changes
2. Left ventricular strain or digitalis effect, or both
3. Right ventricular strain or digitalis effect, or both
4. Anterior wall injury
5. Posterior wall injury
6. Lateral wall injury
7. Inferior wall injury
8. T wave abnormality in lead X, Y or Z

* These prior probabilities are in essence a weighting factor based on the previous experience of making any given diagnosis in a particular population. Although the use of the Bayesian approach in medical diagnosis is much debated, the significant improvement in electrocardiographic diagnostic accuracy of the Veterans Administration program depends on the proper use of these prior probabilities, as noted by Pipberger et al.[13]

TABLE II

Clinical Criteria for Determination of Diagnostic Accuracy (507 patients)

Left ventricular hypertrophy (no. = 109)
- Hypertension, 2 year history of blood pressure averaging 170/110 mm Hg or greater, and presence of S_4
- Valve disease
  - Aortic stenosis: valve area <0.8 cm^2
  - Mitral insufficiency: 3+ regurgitation and/or S_3 or increased left atrial size

Myocardial infarction (no. = 94)
- Characteristic clinical history and enzyme abnormality and/or angiographic evidence of marked segmental hypokinesis or akinesis

Right ventricular hypertrophy (no. = 9)
- Mean pulmonary arterial pressure >40 mm Hg

Chronic pulmonary disease (no. = 31)
- FEV_1 <65 percent and PO_2 <70 mm Hg

Left ventricular hypertrophy + myocardial infarction (no. = 15)

No cardiovascular disease (no. = 252)

FEV_1 = forced expiratory volume in 1 second.

(3) *major disagreement*, which included all other differences. This method (Fig. 2) also allowed for the evaluation of cases with multiple abnormalities.

Results

Physician/Computer Agreement

The overall level of agreement is shown in Table III. Complete agreement of the physician and the computer on interpretation of the tracing occurred in 58 percent of cases at the general reviewer level (step 1) and in 63 percent of cases when the reviewers were more familiar with the computer program (step 2). At least half of the disagreements were minor, allowing for an acceptable interpretation in 82 and 84 percent, respectively, of tracings read in steps 1 and 2. Many minor disagreements, particularly on repolarization abnormalities, occurred because many fewer diagnostic categories are used in the Veterans Administration program than in conventional interpretation.

TABLE III

Veterans Administration Program (version 3.4): Physician/Computer Agreement (no. = 1,000 cases)

Degree of Agreement	Step 1	Step 2
Complete	58%	63%
Acceptable interpretation*	82%	84%

* Complete agreement + minor disagreement.

Assessment of physician agreement for individual diagnostic categories: This assessment was undertaken utilizing only the interpretative impression of the step 2 reviewers who analyzed the XYZ lead records in addition to the 12 lead data. Of the total number of tracings reviewed, 38 percent had some abnormality that did not involve probability analysis. For these categories listed in Table IV, complete agreement was present in 67 percent. Failure to note marked left axis deviation as well as nonspecific repolarization abnormalities accounted for the majority of the disagreements. (In more recent versions of the program,

```
ID          01023095                DATE        11/66/74
RACE        WHITE                   AGE         40-49
WEIGHT      170                     DIGITALIS   NO

CONSIDER SINUS ARRHYTHMIA
POSSIBLE APC#S
QRS AXIS   24  DEG
HEART RATE   70/MIN          9  QRS

** TIME INTERVAL  (SEC)
    PR INTERVAL      QRS-DURATION      QT INTERVAL
      .154              .046              .383

** DIAGNOSTIC STATEMENT
   ** P-QRS-T
      INFERO-POSTERIOR INFARCTION                    93.5
      LAO                              98.5
   ** RHYTHM
      CONSIDER SINUS ARRHYTHMIA
      POSSIBLE APC#S
```

FIGURE 1. Modified printout for the Veterans Administration program as used at the Minneapolis Veterans Administration Hospital. Orthogonal XYZ lead measurements are omitted and the general format has been rearranged. For this particular example, APC ± S = atrial premature complexes and LAO = left atrial overload. The numbers beside the diagnostic statements represent the probability values for these diagnoses.

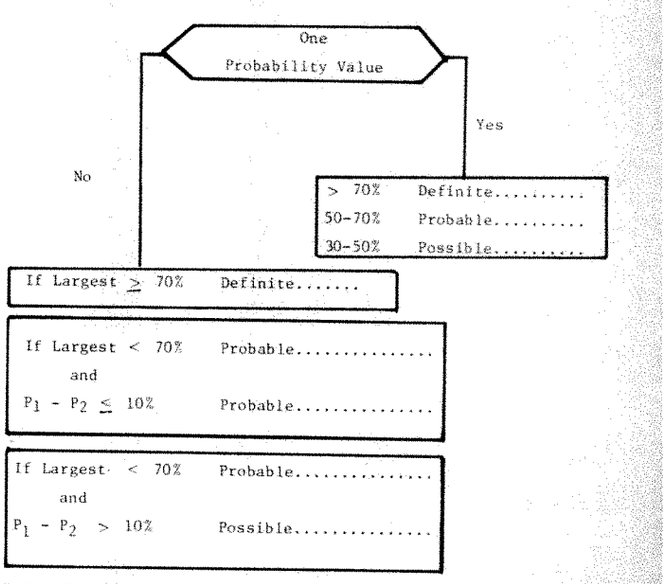


FIGURE 2. Algorithm for conversion of probability values to equivalent English language statements. Multiple probabilities are required to share the total of 100 percent; $P_1 - P_2$ represents the percent difference between the largest probability and any other value.

PHYSICIAN—PROGRAM INTERAGREEMENT

PROGRAM \ PHYSICIAN	Normal	LVH	RVH	BVH	AMI	LMI	PDMI	PE	LVCD	LVCD MI	RVCD	RVCD MI	VH-MI	PE-RVH	OTHER*	TOTAL
Normal	377	8	2	2	6	1	2	1			1				55	455
LVH	16	53		1	3		1	1					2		22	99
RVH	1	1	3				1								7	13
BVH	2	1		4											3	10
AMI	2	1			35								1		2	41
LMI						5										5
PDMI	8			2			81				2	2			12	107
PE				1	1			8							7	17
LVCD									6							6
LVCD & MI	1	5					1		3	17					1	28
RVCD							1				15	3				19
RVCD & MI											4	5			2	11
VH-MI	3	3	1		2		4						15		12	40
PE-RVH	3						1	1						2	9	16
OTHER*	9	7			1		1								115	133
TOTAL	422	79	6	10	48	6	93	11	9	17	22	10	18	2	247	1000

FIGURE 3. Physician-program agreement. AMI = anterior myocardial infarction; BVH = biventricular hypertrophy; LMI = lateral myocardial infarction; LVCD = left ventricular conduction defect; LVH = left ventricular hypertrophy; MI = myocardial infarction; PE = pulmonary emphysema; PIMI = posteroinferior myocardial infarction; RVCD = right ventricular conduction defect; RVH = right ventricular hypertrophy; VH = ventricular hypertrophy.

*Primary significant diagnoses of atrioventricular block, S-T T wave abnormality, arrhythmia or pathologic axis deviation, already mentioned in Table IV, are introduced here n the misclassification matrix. For example, there were 12 cases defined by the program as "left ventricular hypertrophy" which the reviewer defined as left axis deviation or ST-T wave changes without left ventricular hypertrophy.

TABLE IV

Significant Program Measurement and Rhythm Errors Based on Physician Interpretation

	Abnormality Present	Abnormality Missed	Abnormality Overcalled
ST-T abnormality	157	52	12
A-V block			
First degree	56	2	1
Second degree	2	1	. . .
Pathologic left axis deviation (>−30°)	45	29	. . .
Pathologic right axis deviation (>+110°)	14	1	. . .
A-V junctional rhythm	2	. . .	14
Atrial fibrillation	30	2	4
Premature ventricular complexes	21	4	. . .
Premature supraventricular complexes	35	1	. . .
Idioventricular rhythm	3	1	. . .
Total	365	107	17

A-V = atrioventricular.

the algorithms for detecting these abnormalities, the left axis deviation and nonspecific ST-T changes have been updated and give better results.)

Figure 3 shows the distribution of agreement and disagreement on the electrocardiograms whose primary diagnosis mainly involved probability analysis. Four hundred twenty-two of these electrocardiograms were considered normal by the physician. In 377 of these "normal" tracings the same interpretation was made by the computer program (agreement rate 91 percent). Among the 45 tracings in which the interpretations differed, differences in diagnosed left ventricular hypertrophy (16 tracings) and posteroinferior infarction (8 tracings) accounted for most of the disagreement. Five hundred seventy-eight electrocardiograms were considered abnormal by the physician reviewers, the computer agreeing on 349 (61 percent). The program category noted for each tracing was considered to represent its primary diagnosis. Most tracings with an abnormal QRS configuration had a primary diagnosis of either left ventricular hypertrophy or myocardial infarction, or both. The rate of agreement was relatively high for the diagnosis of myocardial infarction but was considerably lower for left ventricular hypertrophy. A wide range in the degree of agreement was observed among the various diagnostic categories, suggesting considerable potential for improvement in accuracy.

TABLE V

Determination of Accuracy by Nonelectrocardiographic Criteria

	Physician		Program		Agreement*
	S	R	S	R	
Left ventricular hypertrophy (no. = 109)	43%	69%	69%	78%	51%
Myocardial infarction (no. = 94)	56%	69%	76%	79%	60%
Chronic pulmonary disease (no. = 31)	23%	60%	45%	65%	26%
No cardiovascular disease (no. = 252)	86%	. . .	79%	. . .	79%
Total (no. = 507)	65%	. . .	73%	. . .	66%

* Agreement represents the *mutual agreement* of both physician and program with the true clinical diagnosis established from independent criteria.

R = reliability = (sensitivity + specificity)/2; S = sensitivity.

Physician Versus Computer Diagnostic Accuracy

For an assessment of diagnostic accuracy, we selected 507 of the computer-processed tracings in which the diagnosis could be reliably established from clinical data in accordance with the criteria listed in Table II. Because the majority of the patients with cardiovascular disease had clinical conditions that would result in either left ventricular hypertrophy, myocardial infarction or chronic pulmonary disease, the determination of accuracy for categories of abnormality was limited to these groups (Table V). False positive diagnoses for any of these categories were obtained from the group noted to have no cardiovascular disease. The overall diagnostic accuracy rate of the computer program was 73 percent, a rate significantly higher than 65 percent rate achieved by the step 2 reviewers utilizing conventional criteria. A significant improvement in accuracy by the computer program was observed for both left ventricular hypertrophy and myocardial infarction. In these categories the mutual agreement of the program's diagnosis and the physician's diagnosis with the clinical reference was relatively low, reflecting the independence of each interpretative approach. Results of both sensitivity and reliability for chronic pulmonary disease were quite low for both the program and the physician. Although the sensitivity was higher for the program it is difficult to evaluate these results in view of the small sample available for analysis.

In the category of no cardiovascular disease the physician reviewers made significantly fewer interpretative errors than did the computer program. Fifty-

TABLE VI

Effect of Adjustment of Probability Value of Diagnostic Reliability

	Initial Prior		Adjusted Prior		Initial later		Adjusted Later	
	S	R	S	R	S	R	S	R
Left ventricular hypertrophy	69%	78%	73%	82%	69%	78%	67%	77%
Myocardial infarction	76%	79%	. . .	. . .	76%	79%	66%	80%

R = reliability = (sensitivity + specificity)/2; S = sensitivity.

TABLE VII

Comparative Accuracy of Atrial Analysis

	Physician		Program	
	S	R	S	R
Left atrial overload (no. = 60)	17%	56%	38%	62%
Right atrial overload (no. = 12)	17%	52%	50%	54%

R = reliability = (sensitivity + specificity)/2; S = sensitivity.

three tracings in this category were erroneously interpreted as abnormal by the program, including 36 tracings with an incorrect diagnosis of either left ventricular hypertrophy (no. = 18) or posteroinferior myocardial infarction (no. = 18). Because these two categories had the greatest number of misdiagnoses we attempted to increase their recognition by adjusting the prior probability values (Table VI). Review of our own hospital electrocardiographic experience indicated that 0.42 was a more appropriate prior probability value for left ventricular hypertrophy in the presence of hypertension than the 0.54 value utilized by the Washington, D.C. Veterans Administration Hospital. However, we found no significant difference for myocardial infarction in the presence of coronary artery disease (0.53). We also decided to determine the extent to which utilization of a higher level of later probability would affect reliability, and accordingly the threshold value was increased from 30 to 45 percent.

These results are noted in Table VI: The adjustment of prior probabilities increased both sensitivity and specificity for left ventricular hypertrophy. However, after modification of the later probability level, there was no change in diagnostic performance for left ventricular hypertrophy; for myocardial infarction, there was 1 percent increase in reliability arising from a greater specificity but at the expense of a 10 percent decrease of sensitivity.

The recognition of atrial abnormality is also based on probability analysis in the Veterans Administration program. Because this aspect of the program underwent several modifications during the course of the study we chose to evaluate only the accuracy of the most recent revision. Of the original 507 tracings selected for accuracy analysis, 175 were in this category. The interpretation of left atrial overload was assumed if severe hypertension, myocardial infarction, congestive heart failure or significant aortic valve disease was present. The presence of severe chronic lung disease was considered a basis for right atrial overload. On the basis of these criteria 60 tracings were considered to have left atrial overload, 12 to have right atrial overload and 103 to have evidence for atrial disease (Table VII).

Discussion

Recently, Bailey et al.[19,20] designed an interesting method of testing the reproducibility of computer programs for electrocardiographic interpretation. The Veterans Administration program (AVA 3.4) has shown excellent results in this regard, but its clinical acceptability and diagnostic accuracy have not been assessed in an independent clinical setting.

In general, evaluations of the diagnostic performances of computer programs for electrocardiographic interpretation have utilized physician agreement as an index of accuracy.[2,3,9,21] The degree of similarity between the criteria utilized by the reviewers and those of the computer program,[22] has had a major effect on most studies. When these are different, considerable disagreement in interpretation can be expected. Much of the disagreement seems to be related to the lack of standardization of electrocardiographic criteria, which may be a major obstacle to obtaining a consensus in assessment of any given program of electrocardiographic analysis.[23] The assessment of a computer program must also take into consideration other factors that may affect observer variation.[24] Most evaluations have used only experienced cardiologists as reviewers; however, we attempted to address in addition the program of general user acceptability.

The use of statistical decision-making in electrocardiographic analysis is a departure from that technique of most commonly used computer programs. Although the statistical method has the advantage of avoiding the constraints of deterministic algorithms, there is a psychologic disadvantage of not utilizing the traditional electrocardiographic interpretative language familiar to the physician. In the case of the Veterans Administration program, this problem of acceptance could be effectively resolved by the relatively simple expediency of changing the language format of the interpretation printout. Subsequently the primary complaint was related to constraint on the number of diagnostic categories, some of which was related to the well recognized redundancy of language in traditional electrocardiographic interpretation. From the standpoint of recognizing the major diagnostic abnormalities the degree of agreement was not significantly different from that of other commonly used programs that rely on traditional criteria.

Standards for diagnostic accuracy: Although a high level of agreement with physician interpretation facilitates physician acceptance, it does not necessarily assure a high degree of diagnostic accuracy. Most clinical electrocardiographic criteria commonly utilized have had limited validation, particularly in varied population settings. This has been borne out by observations such as that of Simonson et al.,[10] which revealed low levels of diagnostic accuracy even when electrocardiograms were interpreted by physicians considered to have the highest level of expertise. For certain diagnostic categories, particularly hypertrophy and infarction, it is therefore essential to use nonelectrocardiographic data for validation. Traditionally, autopsy material has been considered the most reliable independent standard. However, with improvement in clinical methodology it has been possible to develop a data base that can reliably serve as a basis for validation

of many of these categories of electrocardiographic abnormalities.

The use of these standards independent from the electrocardiogram for validation is even more important in regard to the Veterans Administration program in that the interpretations are based entirely on statistical decision and in no direct way relate to conventional criteria.[25] Using this approach in our analysis of all abnormal electrocardiograms, we found a significant improvement in sensitivity over that achieved with conventional criteria. Furthermore, the assessment of interpretative results in patients with no cardiovascular disease indicated that the improvement in sensitivity could be achieved with an acceptable level of specificity. These results would indicate the potential of such a statistical decision program for improvement in accuracy in certain diagnostic categories over that attainable with conventional criteria.

"Prior probabilities" approach: A most interesting feature of the Veterans Administration program is the use of "prior probabilities." This approach implies that specific prior probabilities must be determined for each substantially different population to which the program is applied. Generally this can be considered a flexible feature of the program that allows for the ability to modify reliability. In this evaluation, our initial assumption of equal prior probabilities for the Washington and the Minneapolis Veterans Administration populations was not entirely correct in that our prevalence of left ventricular hypertrophy was less than that in Washington and subsequently the use of a corrected prior value improved the reliability of the diagnosis. Although adjustment for the type of population is most important in obtaining maximal effectiveness of the prior probability, it is also important to assure proper application of the prior probability for each tracing analyzed by correct entry of disease code identification at the time of electrocardiographic reading.

Left atrial overload recognition: Overall a sensitivity of the atrial analysis program is difficult to determine from our data because of the limited sample size. It would appear that recognition of left atrial overload was improved over that achieved by conventional criteria; however, the level of sensitivity was still quite low and there was a high percentage of overcalls for both left and right atrial abnormality.

Clinical implications: We believe that the overall diagnostic performance of the Veterans Administration program is clinically satisfactory. In general a greater degree of physician education is required to achieve acceptance of the program than that required for most programs utilizing conventional criteria. However, the program offers the challenge of improvement in recognition of significant diagnostic information from the electrocardiogram. Of some concern in regard to routine application of the overall program is that it is established from a data base that does not include women and children. Although these groups are now being added to the data pool, use of the present version of the program in a general cross-sectional population would probably be limited. Our results can be considered valid only for populations similar to ours, and further testing of the program will be needed in other population groups to determine a more general applicability.

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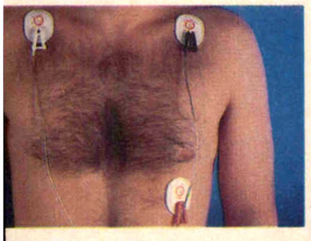
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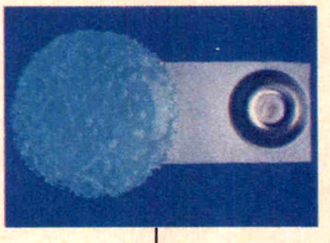
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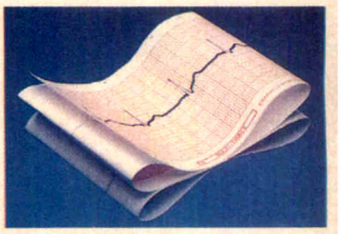
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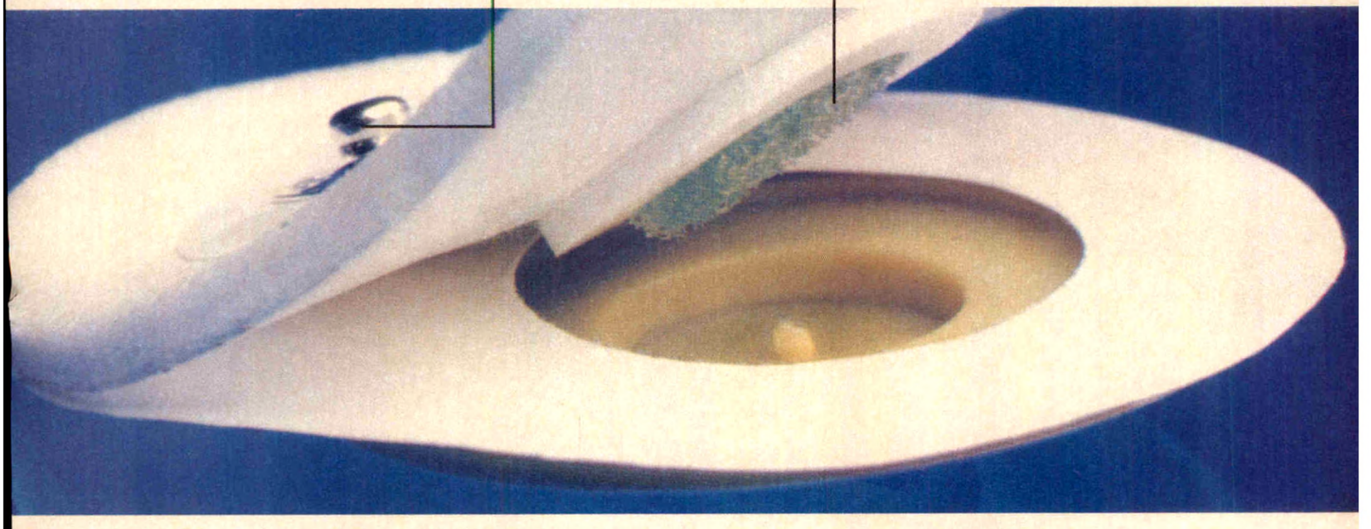
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Dobutrex has minimum effect on ventricular automaticity[3] and does not reduce blood pressure.[4] This, together with its low chronotropic potential, reduces the risk of arrhythmia (see warnings).

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Dobutrex does not have the direct renal vasodilative effect of low-dose dopamine; however, in patients with heart failure, Dobutrex generally promotes a diuresis as renal perfusion rises with the increased cardiac output.[5]

Direct-Acting

Unlike dopamine, Dobutrex acts directly on the myocardium and does not depend on the release of endogenous norepinephrine for its inotropic activity.

Myocardial Oxygen Balance

Increases in coronary heart perfusion due to increased cardiac output, together with a favorable influence on some of the major determinants of oxygen consumption (for example, decreases in left-ventricular filling pressure, decreases in systemic vascular resistance, and a mild chronotropic effect [2,6]), suggest that Dobutrex improves or maintains myocardial oxygen balance.

Infrequent Side Effects

Increases in heart rate, blood pressure, and ventricular ectopic activity have occurred. The drug is contraindicated in patients with idiopathic hypertrophic subaortic stenosis. In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used before therapy with Dobutrex is instituted. For warnings, precautions, and adverse reactions, see the brief summary of prescribing information.

Because of the rapid onset and brief duration of action of Dobutrex, precise adjustment of cardiac stimulation is possible by regulation of the rate of administration. As a result, when undesirable effects arise, temporary discontinuation of the infusion or reduction in dosage will generally reverse the adverse conditions. No additional remedial measures are usually necessary.

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Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates ctrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051 Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

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CPI®'s new Porous Tip Lead encourages living tissue to grow within the electrode, creating a bond between the heart and the MICROLITH®-P programmable pacing system. The remarkable characteristics of this bond allow you to take full advantage of the MICROLITH-P's programmable features.

IMPROVED ELECTRODE STABILITY

The Porous Tip Lead's direct bond with heart tissue resists dislodgement significantly better than conventional leads.

IMPROVED SENSING CAPABILITY

With greatly reduced fibrotic build-up at the electrode site, the new Porous Tip Lead improves sensing capabilities.

IMPROVED ECONOMY OF CURRENT DRAIN

Optimize longevity of the MICROLITH-P through the reduced current drain of the Porous Tip Lead. The small 7.5mm² tip utilizes available energy efficiently without compromising sensing capabilities or patient safety.

COMPATIBLE DESIGN FOR CONSISTENT PERFORMANCE

Never before has a pacing system achieved this high degree of integration with the requirements of the human body.

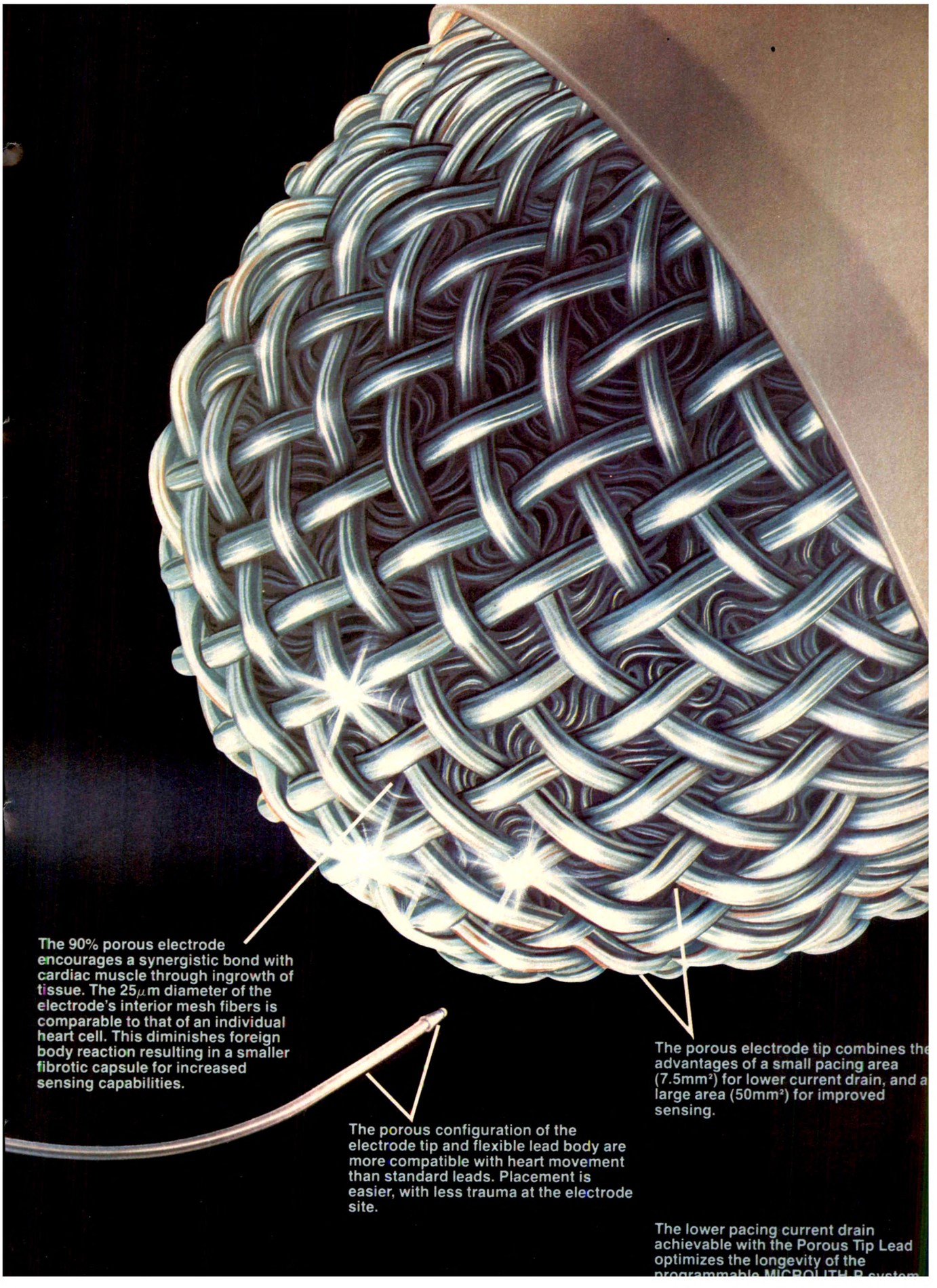
For more information on how MICROLITH-P and the Porous Tip Lead work together to improve pacing reliability and patient care, contact your CPI representative or call Toll-Free (800) 328-9588.



Cardiac Pacemakers, Inc.
4100 North Hamline Avenue
P.O. Box 43079
St. Paul, Minnesota 55164, U.S.A.

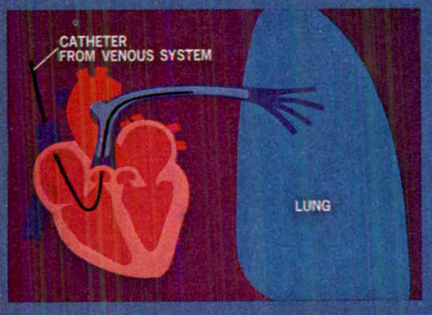
INVOLVED IN MANKIND

©1979 Cardiac Pacemakers, Inc.


The 90% porous electrode encourages a synergistic bond with cardiac muscle through ingrowth of tissue. The 25μm diameter of the electrode's interior mesh fibers is comparable to that of an individual heart cell. This diminishes foreign body reaction resulting in a smaller fibrotic capsule for increased sensing capabilities.
The porous configuration of the electrode tip and flexible lead body are more compatible with heart movement than standard leads. Placement is easier, with less trauma at the electrode site.
The porous electrode tip combines the advantages of a small pacing area (7.5mm²) for lower current drain, and a large area (50mm²) for improved sensing.
The lower pacing current drain achievable with the Porous Tip Lead optimizes the longevity of the

New cardiac catheterization studies demonstrate prolonged changes for over 5 hours in cardiac hemodynamics with PERITRATE® 40-mg ORAL TABLET

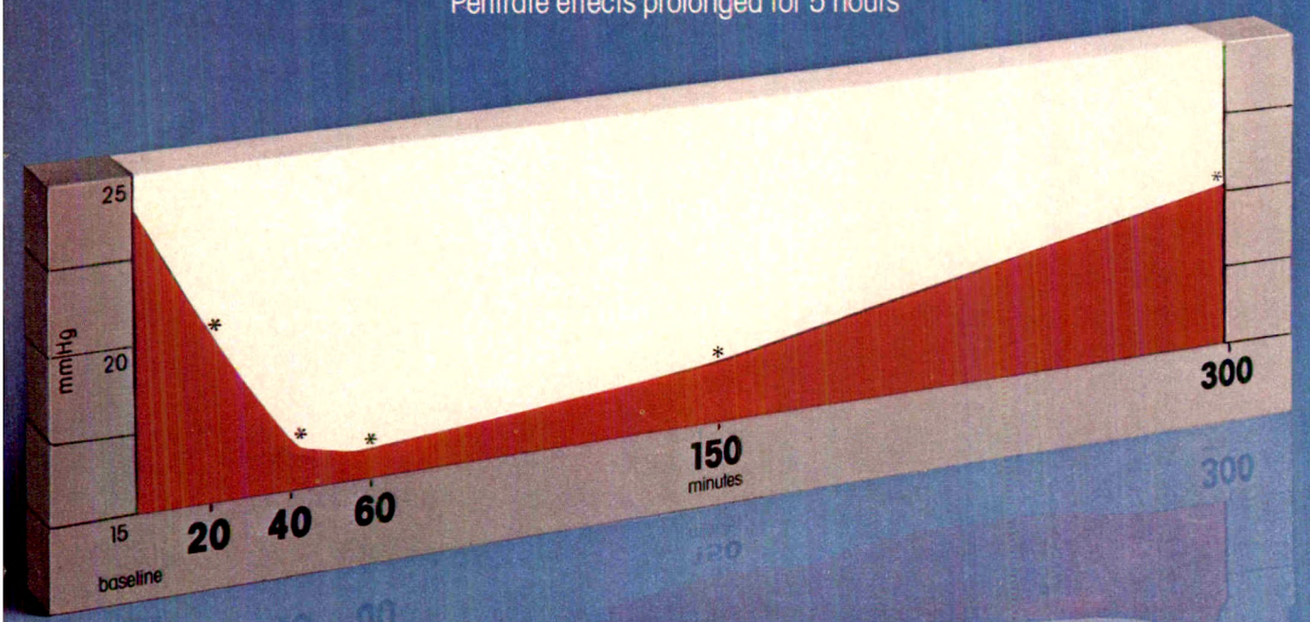
(pentaerythritol tetranitrate)



In a randomized double-blind study of catheterized patients with congestive heart failure, Peritrate 40 mg demonstrated marked changes in a variety of hemodynamic parameters with no change in heart rate.[1]

A marked reduction in PRELOAD: Peritrate reduced pulmonary arterial wedge pressure for over 300 minutes. The maximum reduction was 37%. Pulmonary arterial mean pressure was also reduced for over 300 minutes. These manifestations of reduced PRELOAD resulted from an increase in venous capacitance leading to a reduction in left ventricular end-diastolic volume and pressure. The observed reduction in pulmonary wedge pressure indicates marked preload reduction.

Peritrate effects prolonged for 5 hours



pulmonary arterial wedge pressure (preload)
*Statistically significant at the 5% level.

A reduction in AFTERLOAD: A significant reduction of arterial blood pressure, correlating with reduced AFTERLOAD, was maintained for over 300 minutes.[1]

Reduction in blood pressure for 5 hours

parameter	before Peritrate n=12	60 minutes after Peritrate n=12	150 minutes after Peritrate n=12	300 minutes after Peritrate n=8
blood pressure (mmHg) systolic	122.6	116.7*	116.9	116.8*
	68.7	63.4*	61.3*	61.0*

*Statistically significant at the 5% level.

Peritrate actions observed

- Activity was prolonged for at least 5 hours.
- PRELOAD and AFTERLOAD showed a marked reduction lasting at least 5 hours.

1. Klein RC, Amsterdam EA, Pratt C, et al: Sustained reduction of elevated left ventricular filling pressure in cardiac failure by oral, long-acting nitrate therapy. Presented at The American Federation for Clinical Research, San Francisco, Calif, April 29-May 1, 1978.

Please see following page for brief summary of prescribing information.

Conclusions

1. The prolonged reduction in preload and afterload reduces the amount of energy expended and oxygen consumed by the heart. This reduction in oxygen demand should relieve or prevent angina.
2. Provides a smooth onset of action without tachycardia. Unwanted effects are rare, and patient compliance is excellent.

PERITRATE® 40 mg
(pentaerythritol tetranitrate)

Warner/Chilcott
Division,
Warner-Lambert Company,
Morris Plains, New Jersey 07950

Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) **80 mg**

Peritrate®
(pentaerythritol tetranitrate) **40 mg**

Peritrate®
(pentaerythritol tetranitrate) **20 mg**

Peritrate®
(pentaerythritol tetranitrate) **10 mg**

CAUTION: Federal law prohibits dispensing without prescription.

Description: Each tablet of Peritrate SA Sustained Action contains pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate) is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.

(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.

(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).

Peritrate (pentaerythritol tetranitrate) 40 mg—pink scored tablets in bottles of 100 (N 0047-0008-51).

Peritrate (pentaerythritol tetranitrate) 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also unit dose, package of 10 x 10 strips (N 0047-0001-11).

Peritrate (pentaerythritol tetranitrate) 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

STORE BETWEEN 59° and 86° F (15° and 30° C).

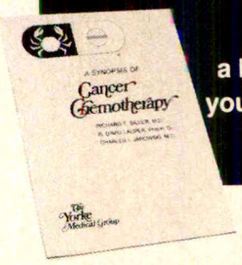
Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.

Full information is available on request.

Warner/Chilcott
Division,
Warner-Lambert Company
Morris Plains, N.J. 07950

PE-GP-82

How to Keep Up with Drug Interaction in Cancer Chemotherapy



Three authorities from a leading medical center show you how to use the most current chemotherapeutic agents

A SYNOPSIS OF

Cancer Chemotherapy

At last a way to keep up with the bewildering proliferation of new chemotherapeutic drugs which have come into use relatively recently. This just published guide will be valuable to every hospital, and every oncology specialist, general internist, clinical pharmacist, and nurse oncologist.

A SYNOPSIS OF CANCER CHEMOTHERAPY is a concise, readily understandable "how to" manual. Developed originally for staff use at The New York Hospital-Cornell Medical Center, the concept proved so successful it was decided to make it available to other professionals. The new users of the SYNOPSIS have the advantage of a proven, time-tested learning system. It is written in a unique, compact work-book style to keep reading time to a minimum.

The reader can quickly find the following for both commercially available and investigational drugs:

- Structure
- Mechanism of Action
- Pharmacokinetics
- Toxicity
- Therapy
- Availability

The chemotherapeutic agents in the main listing section cover these categories:

- Alkylating Agents
- Antimetabolites
- Mitotic Inhibitors
- Antibiotics
- Miscellaneous (includes such drugs as Mithramycin, Mitotane, etc.)

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Chief, Oncology Service, Div. Hematology-Oncology, Clinical Professor of Medicine, Cornell University Medical College, Attending Physician, New York Hospital, Exec. Officer, Cancer & Leukemia Group B.

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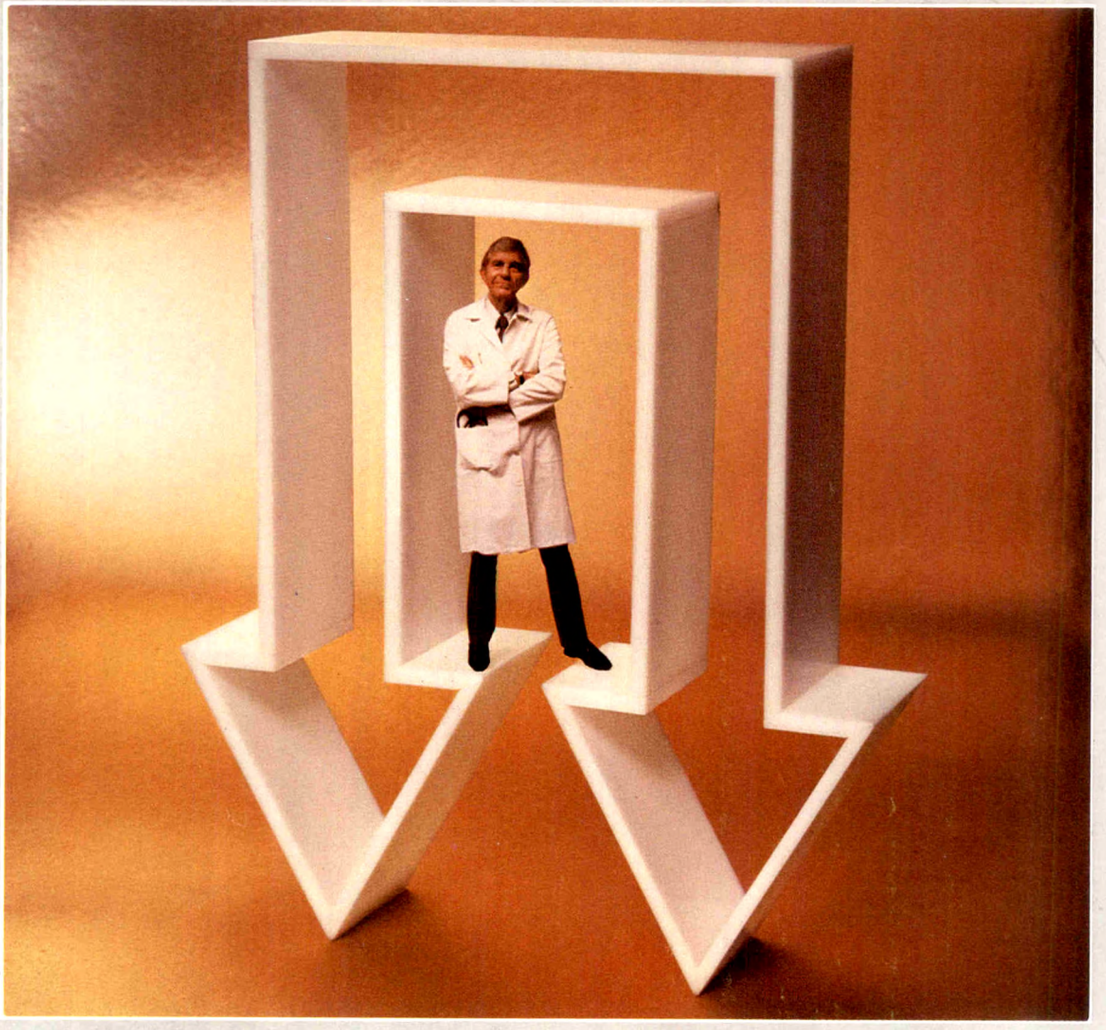
Smith Kline & French Laboratories

NEW

SELACRYN®

BRAND OF ticrynafen 250 mg. Tablet

In Hypertension



Lowers Blood Pressure

Lowers Uric Acid

See next seven pages for more information and prescribing information.

For First-Step Management of Your Hypertensive Patient

NEW **SELACRYN®**

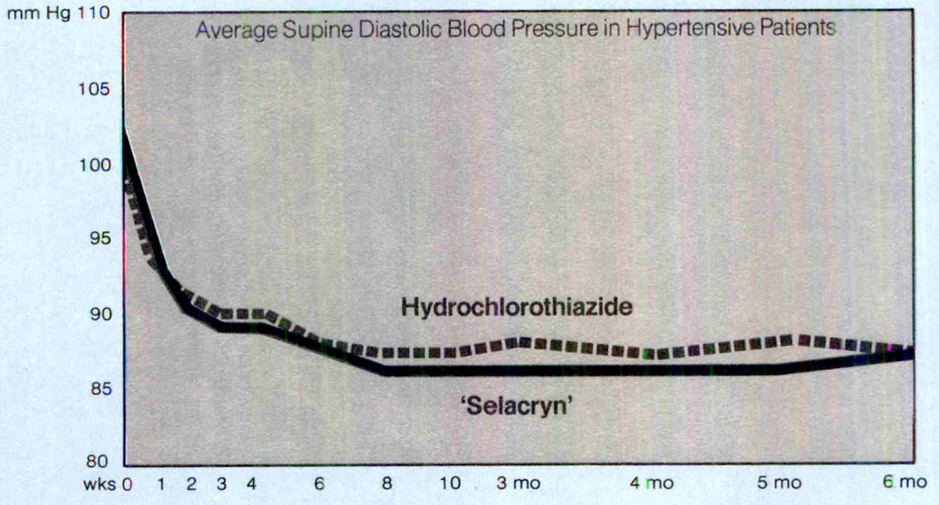
BRAND OF

ticrynafen 250 mg. Tablet

Proven Consistent Reduction of Elevated Blood Pressure... Once-a-Day Dosage[1]

New 'Selacryn' gives your patient the benefits of known, dependable antihypertensive activity. Clinical experience in more than 500 hypertensive patients proves that 'Selacryn' provides all the antihypertensive effect you expect from a diuretic. Double-blind studies establish that 'Selacryn' provides an antihypertensive effect equal to that of hydrochlorothiazide, and that 'Selacryn' exerts its antihypertensive effect when administered once a day. For patients not responding to 250 mg. once daily, dosage may be increased to 500 mg. once daily or 250 mg. administered twice daily.

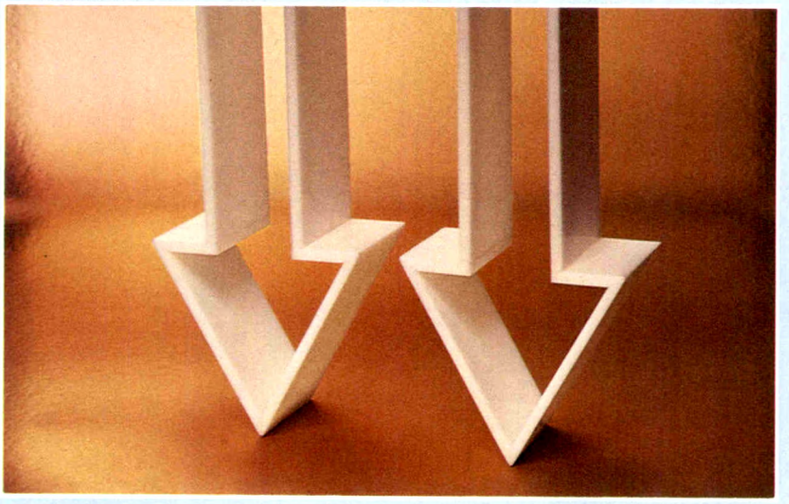
'SELACRYN' vs. HYDROCHLOROTHIAZIDE IN HYPERTENSIVE PATIENTS—SIX-MONTH STUDY



This chart presents results from a six-month multi-center double-blind study involving 71 hypertensive patients receiving 'Selacryn' (250 or 500 mg./day) and 72 hypertensive patients receiving hydrochlorothiazide (50 or 100 mg./day). Active medication was preceded by a one-week drug-free period and two or three weeks on placebo. Differences between the two medications were not statistically significant.[1]

1. Data on file, SK&F Medical Department.

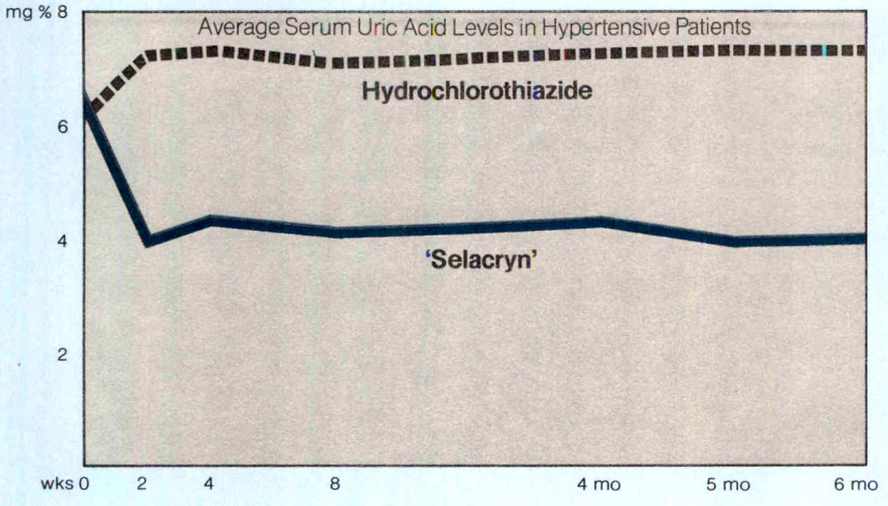
A Single-Entity Diuretic with Two Distinct Actions



Prompt Reduction of Uric Acid in Hypertensive Patients

Because of its uricosuric activity, elevated uric acid is not a concern with 'Selacryn' in the treatment of hypertensive patients. Since uric acid excretion is accompanied by diuresis, urine concentration of uric acid does not increase during 'Selacryn' therapy.

'SELACRYN' (brand of ticrynafen) VS. HYDROCHLOROTHIAZIDE IN HYPERTENSIVE PATIENTS—SIX-MONTH STUDY



Data for this chart were derived from the same six-month multi-center double-blind study described at left.

See following five pages for more information and prescribing information.

For First-Step Management of Your Hypertensive Patient

NEW SELACRYN®

BRAND OF

ticrynafen 250 mg. Tablet

Effective Alone and in Combination with Non-Diuretic Antihypertensives

Once a Day for Initial Therapy and Long-Term Control

'Selacryn' provides all the antihypertensive effect you expect from a diuretic, with the convenience of once-a-day dosage. Clinical experience has consistently demonstrated that the antihypertensive effect of 'Selacryn' is equivalent to that of hydrochlorothiazide. For patients not responding to 250 mg. once daily, dosage may be increased to 500 mg. once daily or 250 mg. administered twice daily.

An Effective Adjunct to Non-Diuretic Antihypertensives

Clinical experience with 'Selacryn' in combination with propranolol, methyldopa and other non-diuretic antihypertensives proves pharmacological compatibility and additive effect. When 'Selacryn' is used with other antihypertensive drugs, the dose of such other agents should be reduced by one-half, initially. Titrate to achieve optimal response.



A New Product You Can Prescribe with Confidence

Comprehensive Testing in Laboratory and Clinic[1]

Thorough testing, in every phase of research, has established both the efficacy and safety of 'Selacryn'. 'Selacryn' has been administered in clinical studies to more than 500 patients with hypertension and 114 with congestive cardiac failure. More than one hundred of these patients have been treated with 'Selacryn' for 12-36 months.

In most respects, the type and incidence of adverse reactions are similar to those seen through the years with the thiazides. Standard laboratory tests you use to monitor the course of thiazide therapy are indicated when you prescribe 'Selacryn'.

Reduce Dosage of Concomitant Oral Anticoagulants

'Selacryn' potentiates the action of oral anticoagulants and should be used with caution with other protein-bound agents. 'Selacryn' causes a decrease in excretion of penicillin.

Maintain Adequate Fluid Intake with Initial Doses of Selacryn®

brand of **tiorynafen**

Initial doses of 'Selacryn' usually produce sufficient diuresis so that supplemental fluids and alkalization of the urine are not ordinarily necessary. Normal intake of fluid should be maintained initially in patients with pre-existing elevated uric acid levels. Patients who are dehydrated, or who are switched to 'Selacryn' from other diuretics, should maintain daily fluid intake of 1500 cc. (48 oz.) for the first three days of therapy.

Potassium Supplements Are Usually Not Necessary

'Selacryn' is similar in kaliuretic effect to hydrochlorothiazide, and potassium supplementation may be advisable in some patients. All patients receiving diuretic therapy should be observed for clinical signs of fluid or electrolyte imbalance.

Some patients who received 'Selacryn' and triamterene have shown marked elevation of BUN and creatinine. Therefore, such a combination is not recommended.

See following three pages for more information and prescribing information.

1. Data on file, SK&F Medical Department.

For First-Step Management of Your Hypertensive Patient

NEW SELACRYN®

BRAND OF

ticrynafen 250 mg. Tablet

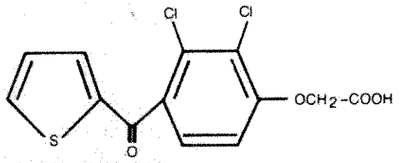
PRESCRIBING INFORMATION

DATE OF ISSUANCE APRIL 1979

Antihypertensive—Diuretic—Uricosuric

DESCRIPTION

'Selacryn' (brand of ticrynafen) is [2, 3-dichloro-4-(2-thienylcarbonyl)-phenoxy] acetic acid.



CLINICAL PHARMACOLOGY

Actions: Three principal actions have been established: antihypertensive, diuretic and uricosuric.

Antihypertensive: 'Selacryn' (brand of ticrynafen) provides a significant and consistent antihypertensive effect at doses of 250 to 500 mg. per day. Little additional antihypertensive effect is obtained at higher doses. Initially, this effect is provided primarily through reduction of plasma volume due to the diuretic properties of the compound. The long-term, consistent antihypertensive effect of 'Selacryn' may involve both renal and extrarenal mechanisms; the exact antihypertensive mechanisms of diuretics are not known. 'Selacryn' does not significantly lower blood pressure in normotensive subjects.

Diuretic: The major site of diuretic action of 'Selacryn', like the thiazides, is in the cortical diluting segment of the distal convoluted tubule of the nephron.

The diuretic and natriuretic effects of 'Selacryn' are dose related through the therapeutic range of 250 mg. once daily to 500 mg. twice daily. Little additional diuretic effect is obtained with higher doses. The diuretic and natriuretic effects begin in one hour after oral administration, reach a maximum in two to four hours, and continue for 12 to 24 hours depending upon the dosage and the individual response of the subject. The urinary excretion of sodium, chloride and potassium produced by 250 mg. of 'Selacryn' is equivalent to that produced by 50 mg. of hydrochlorothiazide.

Uricosuric: 'Selacryn' causes a prompt, consistent reduction in both normal and elevated serum uric acid levels. As with the diuretic activity, the reduction in serum uric acid with 'Selacryn' is dose related through the range of 125 mg. to 250 mg. per day. Little additional uricosuric effect is obtained with higher doses. A 125 mg. dose of 'Selacryn' lowers serum uric acid levels to about the same extent as 500 mg. of probenecid.

Pyrazinamide suppression studies demonstrate that reduction of serum uric acid is produced through inhibition of urate reabsorptive mechanisms at both pre- and postsecretory sites in the proximal tubule, resulting in enhanced urinary excretion of both filtered and secreted uric acid. In crystal equilibration studies in normal volunteers, 'Selacryn', by virtue of its inherent diuretic effect, did not significantly increase the degree of urinary saturation of either uric acid or monosodium urate.

In vitro, 'Selacryn' has no significant inhibitory activity upon xanthine oxidase. There is no enhanced excretion of the oxypurines, xanthines, or hypoxanthines, indicating that 'Selacryn' does not interfere with purine metabolism.

The administration of 'Selacryn' (250 mg.) with other diuretics (hydrochlorothiazide 50 mg., furosemide 40 mg., acetazolamide 500 mg.) can produce additive diuretic and natriuretic effects, while the reduction of serum uric acid and uricosuric effects of 'Selacryn' are maintained.

PHARMACOKINETICS

'Selacryn' (brand of ticrynafen) is rapidly absorbed and is cleared from the body by metabolism and by excretion in the urine. Following administration of 250 mg., significant plasma levels of 'Selacryn' are apparent within one hour, with maximum plasma concentration reached at two to three hours. 'Selacryn' is rapidly cleared from plasma, with a half-life of approximately two hours. 'Selacryn' appears essentially unchanged in plasma although traces of oxidized and reduced metabolites are also present. Approximately 80% of 'Selacryn' is excreted in the urine, 34% as the parent drug.

CLINICAL STUDIES

Hypertension: Double-blind multi-investigator studies were carried out in hypertensive patients with supine diastolic blood pressure of 95-115 mmHg. In short- and long-term studies, 'Selacryn' (brand of ticrynafen) effectively and consistently lowered blood pressure to the same degree as hydrochlorothiazide. The results of representative studies are given below.

Short-Term (Six Weeks) Therapy

	No. Patients	Supine Diastolic Blood Pressure (mmHg.)			Serum Uric Acid (mg.%)		
		Predrug	6 Wks.	Reduction	Predrug	6 Wks.	Change
'Selacryn' (250 mg. once or twice daily)	66	105	92	13	6.1	3.3	-2.8
Hydrochlorothiazide (50 mg. once or twice daily)	59	105	93	12	6.4	8.0	+ 1.6
Placebo	25	103	100	3	6.7	6.6	-0.1

Long-Term (Six Months) Therapy

	No. Patients	Supine Diastolic Blood Pressure (mmHg.)			Serum Uric Acid (mg.%)		
		Predrug	6 Mos.	Reduction	Predrug	6 Mos.	Change
'Selacryn' (250 mg. once or twice daily)	71	101	87	14	6.2	4.0	-2.2
Hydrochlorothiazide (50 mg. once or twice daily)	72	100	87	13	6.1	7.3	+ 1.2

Patients from the double-blind studies were continued on 'Selacryn' (250 mg. or 500 mg. daily); supine diastolic pressure was controlled at levels of 90 mmHg. or less in about 75% of the patients. Approximately 50% of the patients received concomitant therapy with nondiuretic antihypertensive agents such as propranolol or methyldopa.

Congestive Cardiac Failure: Double-blind studies of six to 12 weeks' duration comparing the effects of 'Selacryn' (250 or 500 mg. daily) and hydrochlorothiazide (50 or 100 mg. daily) in patients with congestive cardiac failure of various etiolog showed that 'Selacryn' and hydrochlorothiaz were equally effective in controlling signs a symptoms of congestive cardiac failure. Patie treated with 'Selacryn' had a significant decrea in serum uric acid levels, whereas those treat with hydrochlorothiazide had an increase or significant change in serum uric acid levels.

INDICATIONS

'Selacryn' (brand of ticrynafen) is indicated in management of hypertension, with or without peruricemia, either as the sole therapeutic ag or to enhance the effectiveness of other antihyp tensive drugs in the more severe forms of hyp tension. Because of its uricosuric activi 'Selacryn' will not increase serum uric acid leve as other diuretic agents usually do.

'Selacryn' is indicated in the management of and water retention states associated with cong tive cardiac failure.

Use in Pregnancy. Routine use of diuretics dur normal pregnancy is inappropriate and expos mother and fetus to unnecessary hazard. Diuret do not prevent development of toxemia of pr nancy and there is no satisfactory evidence t they are useful in the treatment of toxemia.

Edema during pregnancy may arise from pat logic causes or from the physiologic and mecha cal consequences of pregnancy. Diuretics indicated in pregnancy when edema is due pathologic causes, just as they are in the abse of pregnancy (however, see WARNINGS belo Dependent edema in pregnancy, resulting from striction of venous return by the gravid uterus properly treated through elevation of the lower tremities and use of support stockings. Use of uretics to lower intravascular volume in instance is inappropriate. During normal pr nancy there is hypervolemia which is not harm to the fetus or the mother in the absence of car vascular disease. However, it may be associa with edema, rarely generalized edema. If s edema causes discomfort, increased recumbe will often provide relief. Rarely this edema cause extreme discomfort which is not relieved rest. In these instances, a short course of diur therapy may provide relief and be appropriate.

CONTRAINDICATIONS

Anuria, severe or progressive renal disease, persensitivity to the drug, and known renal acid calculi.

WARNINGS

Interaction with Anticoagulants: *'Selacr (brand of ticrynafen) potentiates the action of anticoagulants.* Therefore, reduction in the a coagulant dosage is required in patients recei both drugs. *In vitro* studies indicate that 'Selac can compete with warfarin for the same prot binding sites to cause an increase in free warfa

Potassium-Sparing Diuretics: Marked eleva of BUN and creatinine has been seen in some tients who received 'Selacryn' and triamter Therefore, such a combination is not rec mended.

Patients with Impaired Liver Function: 'S cryn', like the thiazides, is not considered ap priate therapy in hepatic ascites and its use is recommended in such patients. In severel hepatic ascites patients treated with 'Selacr elevations of BUN (up to 44 mg.%) and se creatinine (up to 4.5 mg.%) have been obser

Usual Dosage: Once a Day for Hypertension...



Lowers Blood Pressure, Lowers Uric Acid

250 mg. Tablet

evations were not seen in ambulatory cir-atients with mild ascites.

s with Impaired Renal Function: In pa-ith progressive or advanced renal disease, n' may precipitate azotemia. Cumulative f diuretics may develop in patients with im-enal function. Frequent electrolyte, creati-d BUN determinations should be performed therapy and periodically thereafter during nt. If renal impairment progresses, 'Sela-ould be discontinued.

in Pregnancy: There has been no experi-date with the use of 'Selacryn' in pregnant . However, animal studies have demon-that 'Selacryn' crosses the placental bar-ratology studies have shown no effects able to 'Selacryn'. Routine use of diuretics ormal pregnancy is inappropriate and ex-mother and fetus to unnecessary hazard. n' should not be used in pregnant patients n the judgment of the physician the antici-enefits outweigh the potential risks.

g Mothers: It is not known whether 'Sela-excreted in human milk. As a general rule, should not be undertaken while a patient is g since many drugs are excreted in human lacryn' is excreted in the milk of animals.

UTIONS

take: Fluid intake should be increased for three days of therapy (to a total of approxi-500 cc. per day) in patients who may be ted (e.g., patients with excessive alcohol evere vomiting or diarrhea), particularly if nts are hyperuricemic or when 'Selacryn' f ticrynafen) is instituted as a replacement r diuretics. Initial doses of 'Selacryn' usu-duce sufficient diuresis in normal patients supplemental fluids and alkalinization of e not necessary; patients with elevated se-acid levels should be instructed to main-nal fluid intake.

s with Gout: Any drug with uricosuric or activity, including 'Selacryn', may precipi-te attacks of gout. Therapeutic doses of ne are recommended to control the acute during which treatment with 'Selacryn' may nued.

e Metabolism: 'Selacryn' exerts effects on metabolism similar to those observed with diuretics. Insulin requirements may be af-diabetics, and hyperglycemia and glycos-occur in patients with latent diabetes.

erum Creatinine: Elevation of BUN and/ creatinine can occur during diuretic ther-se effects usually revert to baseline values continued therapy or upon withdrawal of .

yte Imbalance: All patients receiving di-erapy should be observed for clinical signs r electrolyte imbalance, i.e., hypokalemia, remia and hypochloremic alkalosis. Peri-termination of electrolytes to detect pos-ctrolyte imbalance should be performed at ate intervals. Serum and urine electrolyte nations are particularly important when the s vomiting excessively or receiving paren-ds. Medication such as digitalis may also e serum electrolytes. Warning signs, irre- of cause, are dryness of mouth, thirst, s, lethargy, drowsiness, restlessness, pains or cramps, muscular fatigue, hypo-tension, oliguria, tachycardia and gastrointestinal disturbances such as nausea or vomiting. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (i.e., increased ventricular irritability). Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease).

Cytotoxic Agents: Drugs with uricosuric activity should be used with caution in patients receiving cytotoxic agents. Since cytotoxic agents result in increased uric acid formation, and some are nephrotoxic, use of cytotoxic drugs with uricosuric drugs requires individualization of dosage and management.

Pediatric Usage: Safety and effectiveness of 'Selacryn' in children have not been established.

DRUG INTERACTIONS

Protein-Bound Drugs: 'Selacryn' (brand of ticrynafen) potentiates the action of oral anticoagulants (See Warnings).

Because *in vitro* studies with tolbutamide, phenytoin (diphenylhydantoin), and warfarin have shown competition for protein-binding sites, caution should be exercised when 'Selacryn' is administered with other drugs that are highly protein bound.

Potassium-Sparing Diuretics: Marked elevation of BUN and creatinine has been seen in some patients who received 'Selacryn' and triamterene. Therefore, such a combination is not recommended

Organic Acids: Like other uricosurics, 'Selacryn' may compete with some compounds for excretion sites in the nephron. This results in decreased excretion and increased plasma levels of these agents. Some of the compounds which may compete with 'Selacryn' for excretion are aminohippuric acid (PAH), penicillin, phenolsulfonphthalein (PSP), and salicylates. 'Selacryn' causes a decrease in the excretion of penicillin and PSP.

Salicylates have a slight inhibitory effect on the uricosuric action of 'Selacryn'.

Lithium: Lithium generally should not be given with diuretics because they reduce its renal clearance and increase the risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy with 'Selacryn'.

ADVERSE REACTIONS

Adverse reactions seen with 'Selacryn' (brand of ticrynafen) in controlled studies were approximately the same as those seen with hydrochlorothiazide. Except where noted, the following adverse effects seen with 'Selacryn' have been reported in a small number of patients, e.g., approximately 1 in 100. **Gastrointestinal:** anorexia, nausea, vomiting, dyspepsia, cramping, diarrhea, constipation; **Central nervous system:** dizziness/lightheadedness (totaled approximately 9 in 100), headache (approximately 4 in 100), paresthesia, syncope, vertigo, somnolence, insomnia; **Cardiovascular:** orthostatic hypotension, palpitation; **Hypersensitivity:** rash, urticaria, pruritus, rare cases of fever and interstitial nephritis, which cleared on withdrawal of the drug, have been reported; however, no causal relationship has been established. **Other:** fatigue/tiredness (approximately 4 in 100), hyperglycemia, glycosuria, muscle cramps, weakness, bitter taste and dryness in mouth. In gouty patients, exacerbation of gout, renal colic or costovertebral pain. Abnormal liver function tests and jaundice have been reported in a few patients treated with 'Selacryn' (brand of ticrynafen); however, no causal relationship has been established.

The following adverse reactions have not been reported to date with 'Selacryn' but have occurred with thiazides or other diuretics: pancreatitis, sialadenitis, xanthopsia, purpura, photosensitivity, necrotizing angiitis, Stevens-Johnson syndrome, respiratory distress, anaphylactic reaction, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, restlessness and transient blurred vision.

DOSAGE AND ADMINISTRATION

Adequate fluid intake should be maintained in normal patients. Fluid intake should be increased for the first three days of therapy in dehydrated patients or in patients in whom 'Selacryn' (brand of ticrynafen) is instituted as a replacement for other diuretics (See Precautions).

Hypertension: The usual adult starting dose is one 250 mg. tablet daily. Depending upon the response of the patient, after two to four weeks dosage may be increased to 500 mg. as a single daily dose or one 250 mg. tablet twice a day.

Although reduction of blood pressure may be seen within two to three days, three to four weeks may be required to achieve optimal therapeutic effect.

When used with other antihypertensive agents, the dose of such other drugs should be reduced by one-half. Titrate to achieve optimal response.

Salt and water retention states *associated with congestive cardiac failure.* The usual adult starting dose is one 250 mg. tablet daily. Depending upon the response of the patient, dosage may be increased to 500 mg. as a single daily dose or one 250 mg. tablet twice a day. Daily dosage should not exceed 1000 mg.

ACCIDENTAL OVERDOSE

Diuretic overdosage may cause excessive diuresis with hypovolemia, postural hypotension and severe electrolyte imbalance. Excessive uric acid excretion with massive doses of 'Selacryn' (brand of ticrynafen) may have the potential of producing urate nephropathy and renal failure. Appropriate therapy for overdosage should include restoration of fluid and electrolyte balance. Alkalinization of urine with sodium bicarbonate should be considered if the acid-base status of the patient permits. When alkali is administered, the acid-base balance of the patient should be frequently monitored by laboratory tests.

HOW SUPPLIED

'Selacryn' (brand of ticrynafen) tablets are supplied as light blue, round, scored, monogrammed tablets of 250 mg. in bottles of 100, and in Single Unit Packages of 100 (intended for institutional use only).

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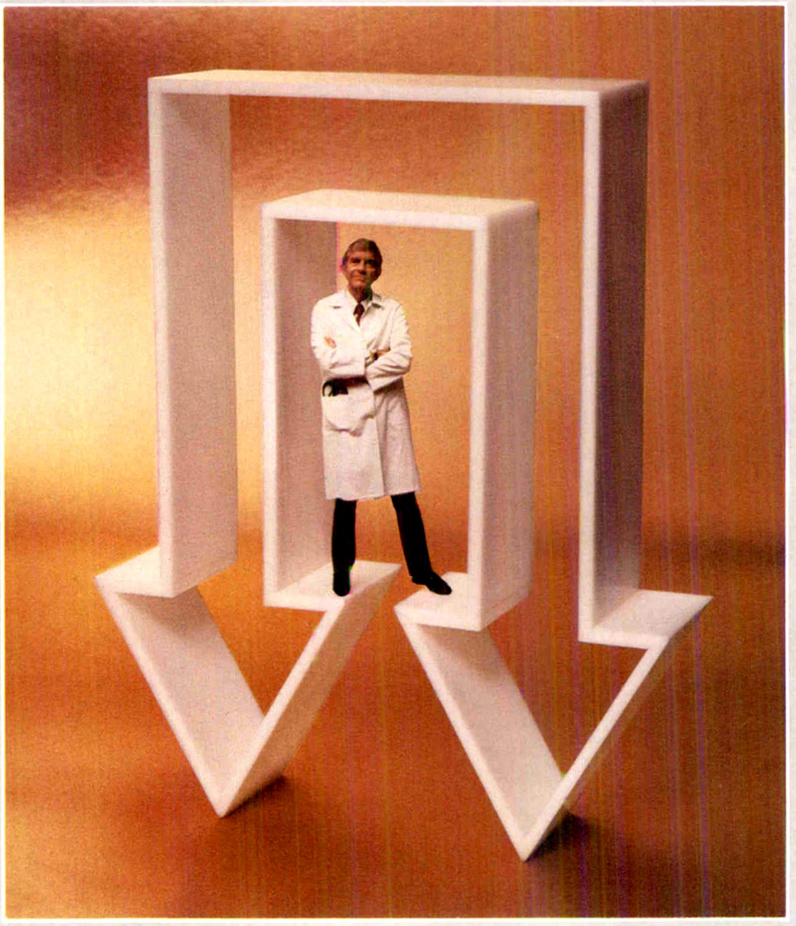
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Management of Surgical Complete Atrioventricular Block In Children

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Because there is disagreement concerning the efficacy of and indication for permanent pacemaker implantation in children with postoperative complete (third degree) atrioventricular (A-V) block, experience in the management of this problem at one institution was reviewed. Thirty-four patients with postoperative complete atrioventricular block were identified. They ranged in age from 4 months to 22 years and in weight from 4 to 60 kg and were evaluated from 1 month to 20 years postoperatively.

Complete A-V block developed within 24 hours of operation in 28 of the 34 patients. A permanent pacemaker was implanted in 13 of the 28. Death occurred in 4 of these 13 patients and in 5 of the remaining 15 patients who did not have an artificial permanent pacemaker. Complete A-V block developed later than 1 day (2 days to 4 months) postoperatively in 6 of the 34 patients; all 6 of these patients survived, and only 3 required permanent pacemaker implantation.

Intracardiac electrophysiologic studies were performed by 14 of the 34 patients. The site of complete block was above the His bundle in 5, within the His bundle in 2, and below the His bundle in 4; it was undetermined in 3. The results of intracardiac electrophysiologic studies are important in delineating the natural history of surgically induced complete A-V block and in the clinical management of this lesion. Permanent pacemaker implantation is indicated if complete A-V block persists longer than 2 weeks postoperatively and if the site of the block is within or below the bundle of His.

Complete atrioventricular (A-V) block is a recognized complication of intracardiac repair of congenital heart defects.[1] It may be transient or permanent. Some patients who have had transient surgically induced complete A-V block later manifest permanent complete block requiring permanent pacemaker insertion.[2] In some instances of surgically induced permanent complete A-V block, the patient may have a supraventricular rhythm adequate to maintain normal cardiac function, may never have episodes of asystole and may not require permanent pacemaker implantation. Many patients with surgically induced complete A-V block will have episodes of asystole and require permanent pacemaker implantation.

It is possible to localize the exact site of complete A-V block with intracardiac electrophysiologic studies.[3] The site of the block may be above, within or below the bundle of His. If one knows the site of the complete block, it may be possible to predict which patients with transient or permanent surgically induced complete block will require permanent pacemaker insertion to prevent asystole.[4,5]

The purpose of this study was to review our experience at the Texas Children's Hospital in the management of patients with surgically induced complete A-V block and to determine whether intracardiac

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electrophysiologic studies are of value in such management.

Methods

Selection of patients: We reviewed the hospital records of all children evaluated in the Section of Pediatric Cardiology, Texas Children's Hospital who had intracardiac operations for a congenital heart defect during the 21 years from 1957 to 1978. Any patient who had documented postoperative complete atrioventricular (A-V) block that persisted for at least 2 weeks or until the patient's death was included in this study.

We identified 34 patients operated on between 1957 and 1978 who had postoperative complete A-V block. Approximately 4,000 patients had intracardiac repair of congenital heart defects in that period of time. (Exactly 2,054 patients had intracardiac repair of congenital heart defects between January 1972 and May 1978. We estimated that 1,946 patients had operations between 1957 and 1972.)

Intracardiac electrophysiologic studies: These were performed in 14 patients by methods previously described.[3,6] The anatomic site of complete A-V block was categorized according to the following method: The block was considered to be above the His bundle if the ventricular depolarization potential was preceded by a His potential and if no His potential was identified after each atrial depolarization potential. If a His potential was recorded after each atrial depolarization potential and a second His potential was recorded before each ventricular depolarization potential, the site of the block was considered to be within the bundle of His (Fig. 1). The site of the block was considered to be below the bundle of His if the ventricular depolarization potential was not preceded by the bundle of His potential but a His potential was recorded after each atrial depolarization (Fig. 2).

Complete A-V block was defined as absence of any evidence of anterograde A-V conduction. This required observation of long strips of electrocardiograms in which P waves occurred at a time when A-V conduction should have occurred, without any variation by shortening of the R-R interval. Patients with sinus bradycardia whose P wave never occurred at a time when conduction could occur were excluded from this study.

Results

Clinical Features

The 34 patients ranged in age from 4 months to 22.4 years (mean 6.3 years) and in weight from 4 to 60 kg (mean 21 kg). These 34 patients have been evaluated from 1 month to 19.7 years (mean 4.2 years) after the onset of complete A-V block. In 7 cases follow-up evaluation has extended to 5 years and in 5 cases to 10 years postoperatively.

Fifteen patients had a ventricular septal defect; one had congenitally corrected transposition of the great arteries with ventricular inversion and ventricular septal defect, six had tetralogy of Fallot, five had an endocardial cushion defect, three had subvalve aortic stenosis (two of these three patients also had ventricular septal defects), two had Ebstein's anomaly, one had aortic stenosis with aortic valve replacement, one had *d*-transposition of the great arteries and one had a secundum type of atrial septal defect. In 28 of the 34 patients complete A-V block developed less than 1 day postoperatively; in the remaining 6 it developed 2 days to 4 months postoperatively.

Treatment

Outcome of treatment in 28 patients who manifested complete A-V block less than 1 day postoperatively (Fig. 3): Temporary pacing wires were inserted in 17 of these 28 patients at the time of intracardiac repair of their congenital heart defect. A permanent pacemaker was implanted in 8 of these 17 pa-

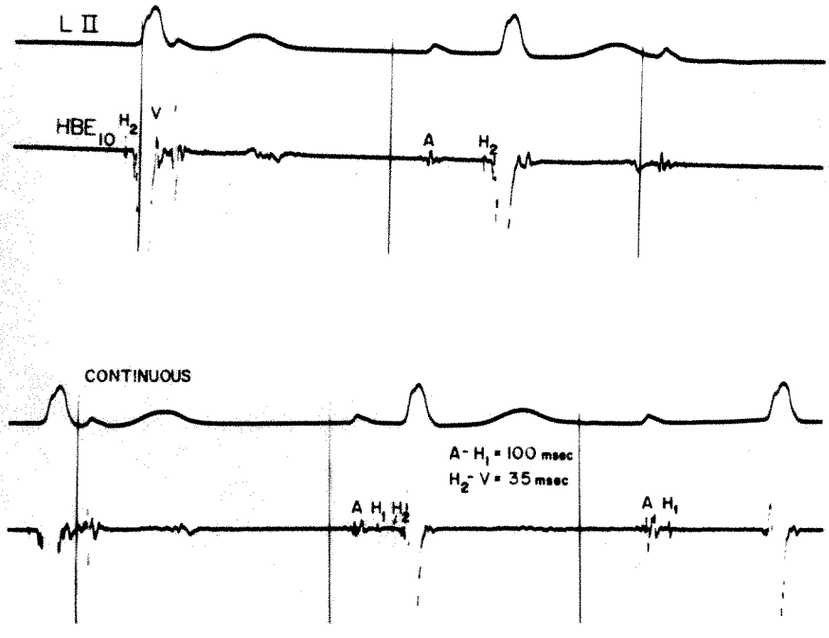


FIGURE 1. Intracardiac electrophysiologic recording from a patient with complete A-V block within the bundle of His. One His potential (H_1) is recorded 100 msec after atrial depolarization and a second His potential is recorded 35 msec before the ventricular depolarization. A = atrial depolarization; H_1 and H_2 = His depolarization; HBE_{10} = His bundle electrogram; L II = surface standard limb lead II; V = ventricular depolarization.

tients; the remaining 9 received no permanent pacemaker. Four of the eight patients (50 percent) with a permanent pacemaker and three of the nine patients (33 percent) without a permanent pacemaker died. Three of the four deaths in the patients with a permanent pacemaker were related directly to an arrhythmia and pacemaker failure. Of the three deaths in patients who had no permanent pacemaker, one was related directly to complete A-V block, one was unrelated to an arrhythmia and the third occurred suddenly at home without documentation of the exact cause.

One patient had temporary pacing wires implanted 4 days after intracardiac repair of tetralogy of Fallot. This patient had a permanent pacemaker implanted 15 days postoperatively and is alive. Temporary pacing wires were not implanted in 10 of the 28 patients. Four of these 10 patients subsequently received a permanent pacemaker; 6 had no pacemaker implanted. All four patients with a permanent pacemaker are alive. Two of the six without a pacemaker died, and in one of these two, death was related directly to complete A-V block.

Outcome of treatment in six patients who had complete A-V block more than 1 day postoperatively (Fig. 4): None of these six patients had temporary pacing wires implanted. A permanent pacemaker was implanted in three of them, and all six patients are alive.

Electrophysiologic Studies

We performed intracardiac electrophysiologic studies in 14 of the 34 patients (Fig. 5). We localized the anatomic site of the complete A-V block above the bundle of His in 5 of the 14, within the bundle of His in 2 and below the bundle of His in 4. The site of the block could not be determined in 3 of the 14 patients.

Complete A-V block above the His bundle (five patients): Only one of these five patients had a permanent pacemaker implanted, and he now has a mechanical pacemaker rhythm. Two of these five patients have sinus rhythm and first degree A-V block, one has

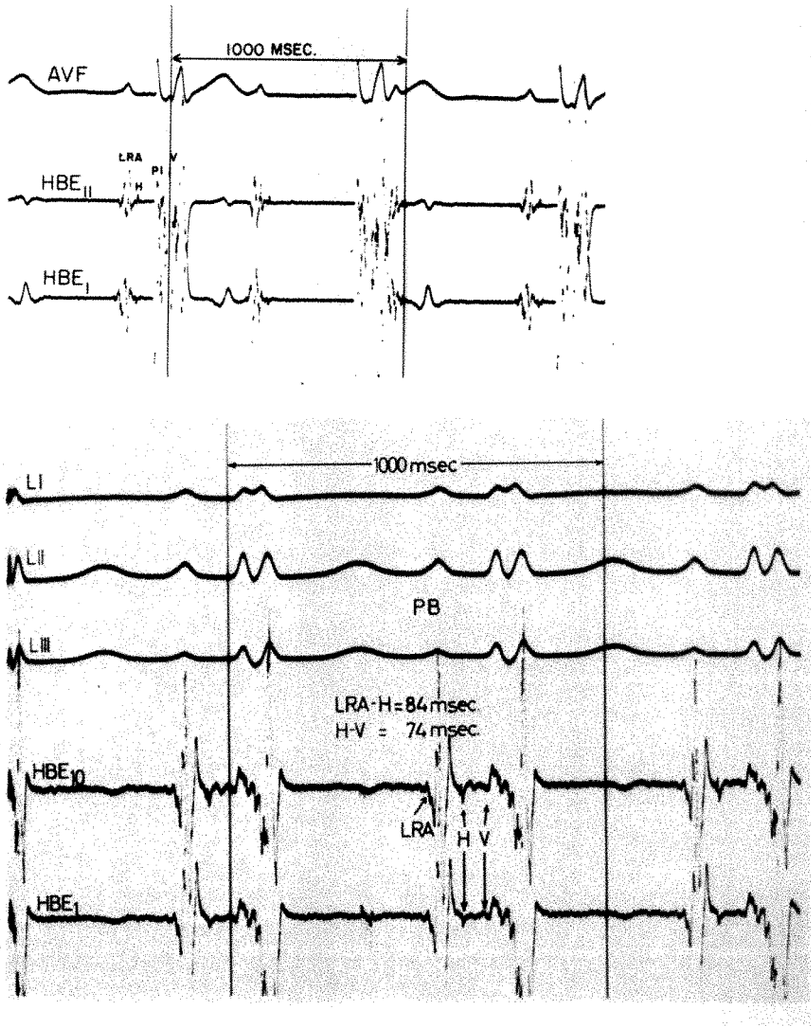


FIGURE 2. Intracardiac electrophysiologic recordings in a child who had intracardiac repair of a ventricular septal defect. **Top,** 14 days postoperatively. The patient has complete A-V block below the His bundle. Each ventricular depolarization (V) is preceded by an artificial pacemaker potential (Pi). Each atrial depolarization potential is followed by a His bundle potential. The atrial to His (H) potential interval is normal. AVF = surface lead aVF; HBE_{II} and HBE_{I} = His bundle electrograms; LRA = low right atrial depolarization. **Bottom,** 12 months postoperatively. The patient now has sinus rhythm with a normal atrial to His potential (LRA-H) interval but a prolonged His to ventricular (H-V) interval.

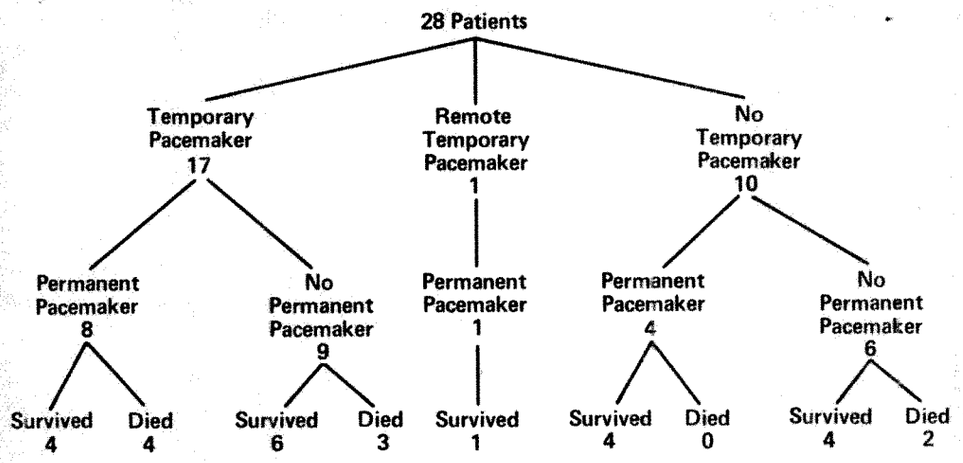


FIGURE 3. Outcome of treatment in 28 patients who had complete A-V block less than 1 day postoperatively.

sinus rhythm and one has complete A-V block and right bundle branch block.

Complete A-V block within the His bundle (two patients): These two patients required a permanent pacemaker and now have a mechanical pacemaker rhythm.

Complete A-V block below the His bundle (four patients): Three of these four patients had a permanent pacemaker implanted and now have mechanical pacemaker rhythm. One patient did not have a pacemaker implanted and now has sinus rhythm, right bundle branch block and left anterior hemiblock.

Site of block unknown (three patients): None of these three patients had a permanent pacemaker implanted. Two of them now have sinus rhythm and right bundle branch block, and one has sinus rhythm with accelerated A-V conduction that was not apparent preoperatively.

Discussion

Reported indications for pacemaker implantation: Disagreement exists about the efficacy of and indication for permanent pacemaker implantation in children with postoperative complete atrioventricular (A-V) block. Lillehei et al.[7] reported that 60 percent of children with chronic surgical complete A-V block died during the first postoperative year and an additional 20 percent died during the subsequent postoperative year.

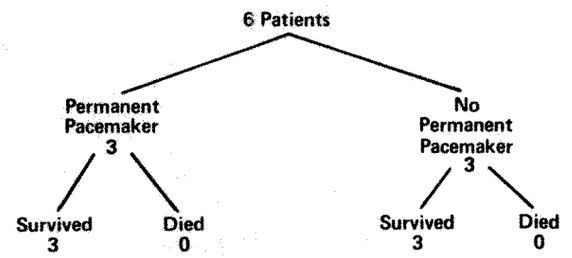


FIGURE 4. Outcome of treatment in 6 patients who had complete A-V block more than 1 day postoperatively.

However, other investigators indicated that the mortality of postoperative complete A-V block was much less. Hurwitz et al.[8] managed 13 children with postoperative complete A-V block that persisted longer than 3 weeks postoperatively. They implanted a permanent pacemaker in 3 of the 13 and 1 of these 3 children died. Of the 10 children managed without a permanent pacemaker, 3 died. These investigators suggested that in selected patients, chronic postoperative complete A-V block could be managed successfully without a permanent artificial pacemaker. Murphy et al.[9] recommended permanent pacemaker implantation only for patients with syncope unresponsive to chronotropic drugs. Stanton et al.[10] recommended pacemaker insertion if (1) complete A-V block persisted longer than 4 weeks postoperatively, (2) Stokes-Adams attacks occurred, or (3) congestive heart failure and low cardiac output occurred secondary to complete A-V block in infancy.

Two major reasons account for the reluctance to implant permanent pacemakers in children: (1) The morbidity from frequent pacemaker battery changes or electrode replacement discourages the use of permanent pacemakers in children. (2) As several investigators have noted, some children with postoperative complete A-V block do not need a permanent pacemaker. Indeed, much of the reported confusion and disagreement concerning the natural history of postoperative complete A-V block in children stems from the variability of its natural history, which probably depends on the exact anatomic site of the block. It is likely that some of the children in our study who died could have been saved by pacemaker implantation. In addition, recent studies of artificial pacemaker reliability in children are encouraging.[11,12] Use of the newer, more reliable permanent pacemakers may lower the high mortality rate of patients requiring artificial permanent pacemakers. All of the patients in our study who died were initially managed more than 4 years ago.

An artificial pacemaker may fail to function for a number of reasons including random component failure, lead breakage or detachment, increased pacing

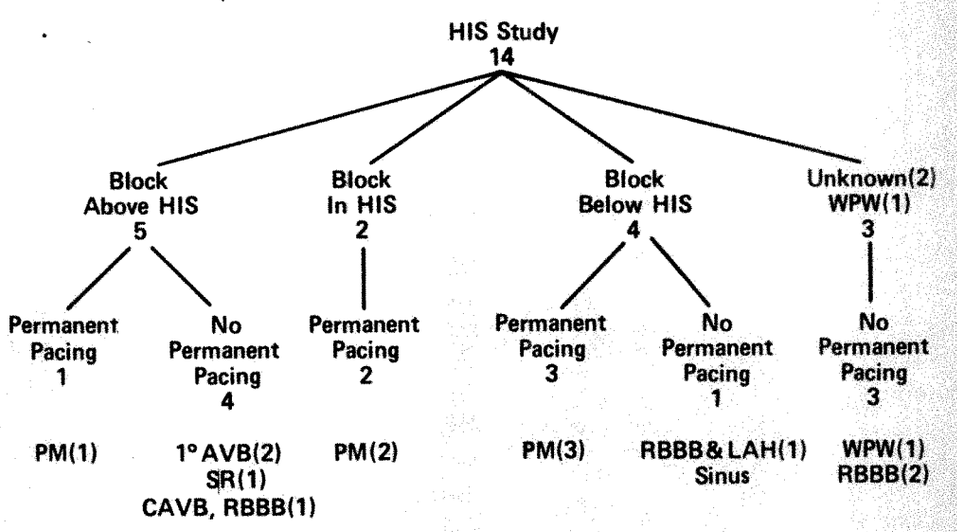


FIGURE 5. Results of intracardiac electrophysiologic studies in 14 patients. CAVB = complete A-V block; 1° AVB = first degree A-V block; LAH = left anterior hemiblock; PM = pacemaker rhythm; RBBB = right bundle branch block; SR = sinus rhythm; WPW = Wolff-Parkinson-White syndrome.

threshold, inadequate sensing with inappropriate stimulation and premature battery depletion. Among our four patients who died with a permanent pacemaker, random component failure occurred in one, sudden death preceded by an arrhythmia in another and failure of ventricular capture in another. The fourth patient died of causes unrelated to pacemaker malfunction.

Recommended management: We propose that children with postoperative complete A-V block who are at risk for asystole or fatal bradycardia can be identified with intracardiac electrophysiologic studies. Indeed all 13 patients with postoperative complete A-V block whom we managed with knowledge of the anatomic site of block are alive.

Our present approach to the management of children with postoperative complete A-V block is summarized in Figure 6. All children with surgically induced complete A-V block should have temporary ventricular pacing wires implanted at the time of operation. External mechanical cardiac pacing can then be employed in the postoperative period if clinically indicated. We allow a 2 week postoperative period of observation for the patient to return to sinus rhythm. Intracardiac electrophysiologic studies are performed 2 weeks postoperatively if the patient (1) continues to have second and third degree A-V block, (2) has sinus rhythm but with a wide (greater than 100 msec) QRS complex, or (3) has first degree A-V block, right bundle branch block and left anterior hemiblock.

We implant a permanent pacemaker in patients with persistent second or third degree A-V block whose site of block is within or below the bundle of His; we do not implant a permanent pacemaker if the site of block

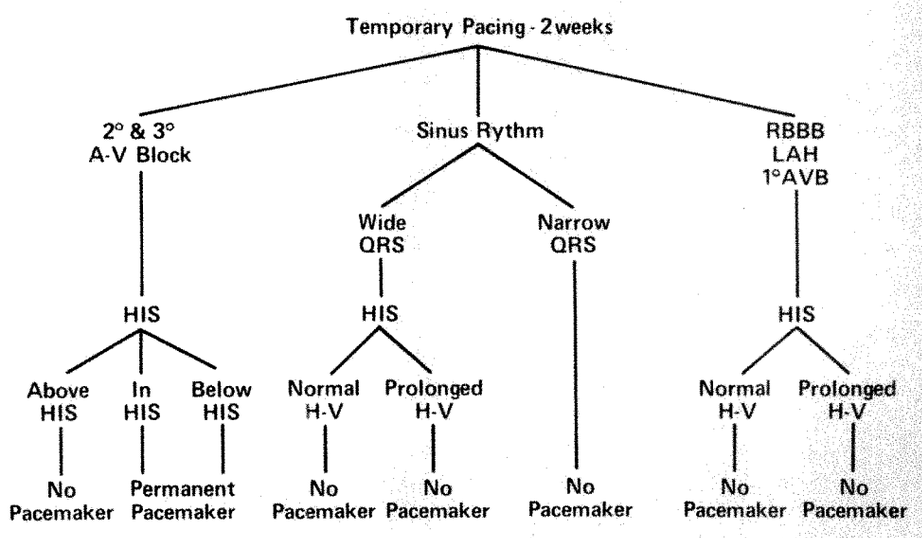


FIGURE 6. Proposed management of surgically induced A-V block. 1° AVB = first degree A-V block; LAH = left anterior hemiblock; RBBB = right bundle branch block.

is above the bundle of His. If the patient has sinus rhythm, a wide QRS complex and a normal His to ventricular interval, we do not implant a permanent pacemaker. Although we do not implant a permanent pacemaker in an asymptomatic patient with sinus rhythm, wide QRS complex and prolonged His to ventricular interval, we observe such a patient closely and recommend pacemaker implantation at the first indication of symptoms referable to complete A-V block.

Similarly, we do not recommend permanent pacemaker implantation for a patient with first degree A-V block, right bundle branch block and left anterior hemiblock and a normal His to ventricular interval. However, in a patient with a prolonged His to ventricular interval, first degree A-V block, right bundle branch block and left anterior hemiblock, we implant a permanent pacemaker if any symptoms occur suggestive of complete A-V block.

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The Fast-Slow Form of Atrioventricular Nodal Reentrant Tachycardia in Children

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An unusual form of atrioventricular (A-V) nodal reentry is described as the underlying mechanism for incessant tachycardia in two children. During tachycardia a fast pathway was utilized for anterograde conduction and a slow pathway for retrograde conduction. This is the reverse of the usual form of A-V nodal reentrant tachycardia, in which the slow pathway is utilized for anterograde conduction and the fast pathway for retrograde conduction. One patient had a smooth ventriculoatrial (V-A) conduction curve demonstrating exclusive utilization of the slow pathway for retrograde conduction. The other had a discontinuous V-A conduction curve demonstrating failure of retrograde fast pathway conduction with resultant slow pathway conduction. In both cases the retrograde effective refractory period of the fast pathway was longer than that of the slow pathway, resulting in the establishment of this unusual reentry circuit. Both patients had a superior P axis with a P-R interval shorter than the R-P interval during tachycardia, features described in a significant number of children with incessant tachycardia. This unusual form of reentrant tachycardia can be suggested by its electrocardiographic pattern and is another mechanism for reentrant tachycardia not previously documented in children.

Electrophysiologic delineation of the mechanisms of supraventricular tachycardia is limited in the pediatric patient.[1–4] Gillette[1] studied 35 children and observed several mechanisms responsible for tachycardia, including reentry through manifest or concealed anomalous pathways, atrioventricular (A-V) nodal reentry, sinoatrial nodal reentry, A-V nodal bypass reentry and atrial and junctional ectopic foci. Others[2–4] have substantiated these mechanisms in infants and children. Clearly, reentry of some type appears to be the mechanism in the majority of cases of supraventricular tachydardia in adults[5–11] and probably in children.

In reentrant tachycardia related to the usual form of dual A-V nodal reentry, a slow pathway is utilized for anterograde conduction and a fast pathway for retrograde conduction.[5,6,8,11,12] Such a pattern was demonstrated in 10 children studied with electrophysiologic techniques.[2,3] The reverse pattern—a fast pathway for anterograde conduction and a slow pathway for retrograde conduction—occurs infrequently in adults[9–11,13–16] but has not been documented electrophysiologically in children. During the electrophysiologic study of two children with resistant supraventricular tachycardia this unusual form of A-V nodal reentry was demonstrated with use of the ventricular extrastimulus technique.

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Methods

Patients

Patient 1: This boy, aged 7 years at the time of electrophysiologic study, had had tachycardia and irregular rhythm in utero. In the years after birth, several physicians remarked about his unusual and fast "heart rhythm," but no further investigation or treatment was recommended because the child was asymptomatic. Eight months before the electrophysiologic study the boy was evaluated by a cardiologist and exhibited a constant tachycardia with momentary intervals of sinus rhythm on multiple examinations. An echocardiogram revealed right and left ventricular dysfunction and left atrial enlargement. The electrophysiologic study was undertaken after the informed consent of the parents was obtained. The patient received Nembutal®, Phenergan®, Thorazine® and Demerol hydrochloride® as premedication.

Patient 2: This infant girl, 5 weeks old at the time of study, was hospitalized at age 2 weeks because of supraventricular tachycardia and was treated with digoxin. Subsequently, she was given propranolol in addition but the combined regimen was unsuccessful in controlling the arrhythmia. Despite the tachycardia, the infant was asymptomatic. An echocardiogram was normal except for a minimal increase in left atrial size. The informed consent of the parents was obtained, and cardioactive drugs were withheld for 48 hours before the study. The infant received morphine sulfate during the study.

Electrophysiologic Studies

In Patient 1, a hexapolar electrode catheter was introduced through an antecubital vein and advanced to the right ventricle. The distal pair of electrodes was utilized for ventricular pacing and the proximal two pairs for high right atrial pacing and high right atrial recordings, respectively. A tetrapolar electrode catheter was introduced into the right femoral vein and positioned across the tricuspid valve for recording low septal right atrial and His bundle electrograms.

In Patient 2, two tripolar catheters were introduced through the saphenous vein. One catheter was utilized for high right atrial and right ventricular pacing and the other for recording low right atrial and His bundle electrograms and for exploring the left and right atria during tachycardia.

In both patients, surface electrocardiographic leads I, II, V_1 and intracardiac electrograms were recorded simultaneously on a multichannel photographic recorder (Electronics for Medicine DR-16) with a paper speed of 100 mm/sec and filter settings of 40 to 500 hertz. Programmed atrial stimulation and rapid atrial pacing were unsuccessful because of the constant supraventricular tachycardia. Consequently, right ventricular pacing was undertaken at 1 or 2 cycle lengths. Ventricular extrastimulations (V_2) were introduced at decremental intervals until the effective refractory period of the ventricle was reached. The stimuli had a duration of 2 msec and were delivered at about twice diastolic threshold with use of a programmed digital stimulator (Biocelestronic, Miami Springs, Florida). Atrial mapping was performed during the tachycardia with recording sites in the high right atrium, low septal right atrium, low lateral right atrium and left atrium, or the left pulmonary artery[17] for the left atrium in Patient 1.

Definitions

Refractory periods and A-V conduction intervals were measured according to methods described by Castellanos et al.[18] A_1, H_1 and V_1 refer to low septal right atrial, His and ventricular deflections, respectively, induced by atrial or ventricular constant-driving stimuli. A_2, H_2 and V_2 refer to deflections induced by premature atrial or ventricular stimuli. The critical A-V or V-A nodal conduction time is the A-H or H-A (A-V or V-A if the H deflection is invisible) interval that induces echo beats or tachycardia.[12,19] Ae represents an atrial echo beat or atrial reentry. During echo beats or tachycardia the ratio of anterograde to retrograde conduction (Ae-H/H-Ae ratio) was determined as described by Akhtar et al.[20] The Ae-H interval was measured from the end of Ae to the beginning of the H deflection in the low septal electrogram; H-Ae is the interval from the end of the H deflection to the beginning of Ae in the low septal electrogram.

During ventricular pacing (V_1-V_1) and ventricular extrastimulation (V_1-V_2), A-V nodal His-Purkinje conduction was substantiated by the production of progressive prolongation of the V-A interval with decremental extrastimuli.[21,22] A discontinuous retrograde conduction (V_1-V_2, V_2-A_2) curve reflects failure of conduction in the fast pathway and institution of conduction over the slow pathway. The retrograde effective refractory period of the fast or slow pathway is the longest V_1-V_2 interval at which V_2 fails to conduct in the respective pathway.[11]

Results

Patient 1: The surface electrocardiogram revealed a supraventricular tachycardia (rate 167/min) and a superior leftward P wave axis (Fig. 1). The P-R interval was short and the R-P interval long, with a P-R/R-P ratio during tachycardia of 0.43.

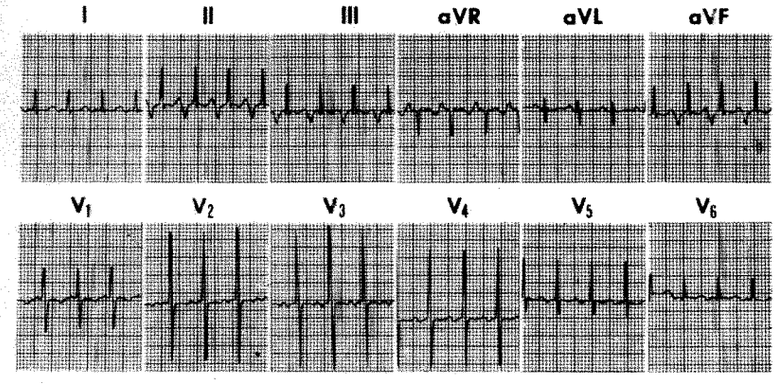


FIGURE 1. Case 1. Twelve lead electrocardiogram reveals supraventricular tachycardia (rate 167/min). P waves are inverted in leads II, III and aVF. The P-R/R-P ratio is 0.43.

The electrophysiologic study demonstrated a smooth V-A conduction curve (V_1-V_2, V_2-A_2) at a driving cycle length of 600 msec (Fig. 2). The slow pathway was utilized exclusively for V-A conduction, and its refractory period was 310 msec. There was progressive prolongation of V-A conduction time with decremental ventricular extrastimuli characteristic of retrograde A-V nodal–His-Purkinje system conduction. The zone of tachycardia encompassed V_1-V_2 intervals between 400 and 320 msec; induction of tachycardia appeared to be dependent on these critical coupling intervals. Figure 3 reveals that tachycardia was not induced at a coupling interval (S_1-S_2) of 410 msec (panel A) but was induced at a coupling interval of 400 msec (panel B). During tachycardia there was retrograde activation with a low septal to high right atrial sequence (Fig. 4A); the ratio of anterograde to retrograde conduction time (Ae-H/H-Ae ratio) was 0.12. Low lateral right atrial and left atrial activation recorded from the left pulmonary arterial position occurred after low septal right atrial depolarization (Fig. 4, A and B). Tachycardia could be terminated by ventricular extrasystoles.

Patient 2: The electrocardiogram (Fig. 5) revealed supraventricular tachycardia at a rate of 188/min and a superior P

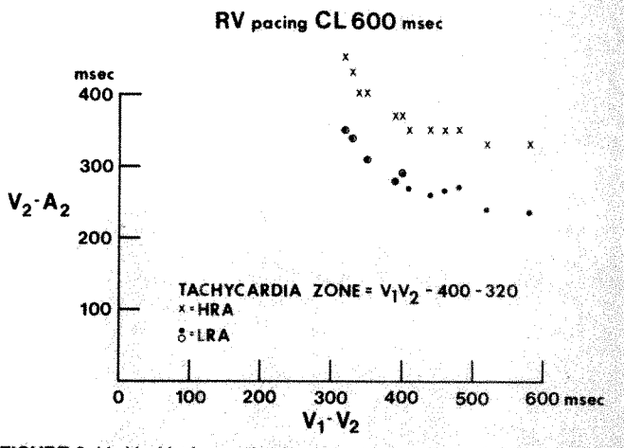
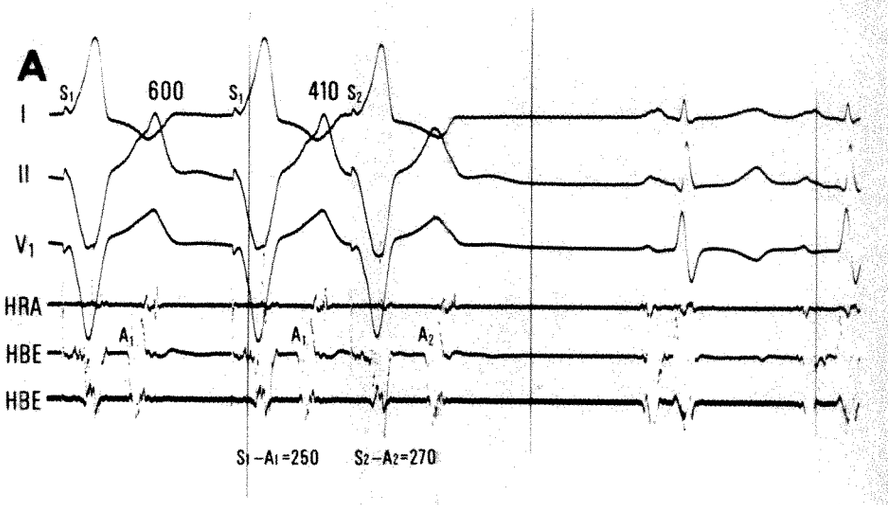


FIGURE 2. V_1-V_2, V_2-A_2 conduction curve during right ventricular (RV) pacing at a cycle length (CL) of 600 msec. **Solid dots** represent low septal right atrial (LRA) activity; **circled dots** represent the tachycardia zone (400 to 320 msec); crosses refer to high right atrial activity (HRA). The V_1-V_2, V_2-A_2 curve is continuous, with retrograde conduction time ranging between 230 and 340 msec.



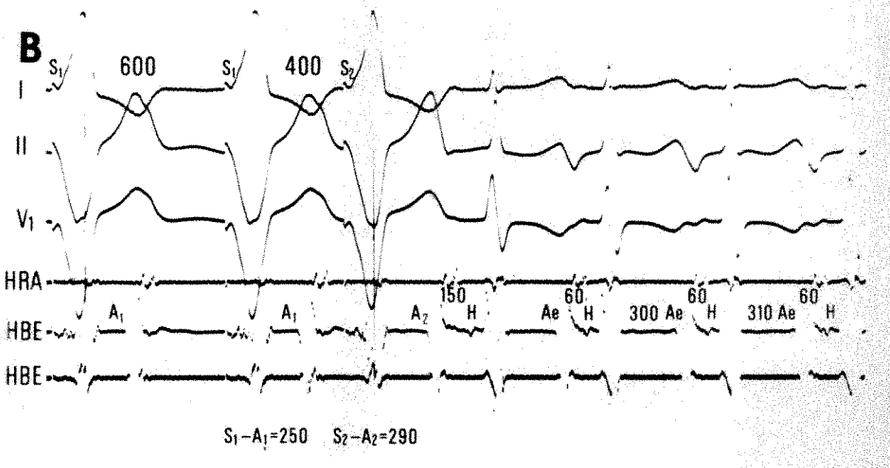


FIGURE 3. Case 1. **A,** ventricular extrastimulus (S_1-S_2) delivered at 410 msec with a right ventricular pacing cycle length of 600 msec (S_1-S_1). Tachycardia is not induced. V-A conduction time with basic pacing (S_1-A_1) is 250 msec; V-A conduction time with the ventricular extrastimulus (S_2-A_2) is 270 msec. **B,** ventricular extrastimulus (S_1-S_2) delivered at 400 msec produces supraventricular tachycardia. V-A conduction time with basic pacing (S_1-A_1) is 250 msec; V-A conduction time with the ventricular extrastimulus (S_2-A_2) is 290 msec. After tachycardia is established the ratio of anterograde (Ae-H) to retrograde (H-Ae) conduction is 60/300. HBE = His bundle electrogram or low septal right atrial electrogram; HRA = high right atrial electrogram.

wave axis. The initiation of the tachycardia occurred with a normal sinus beat and terminated with a QRS complex that followed on a retrograde Wenkebach period (progressive prolongation of the R-P interval) reflecting block in the retrograde V-A pathway (lead II, Fig. 5). During tachycardia the P-R interval was short and the R-P interval long, with a P-R/R-P ratio of 0.5.

The electrophysiologic study revealed a discontinuous V-A conduction curve (V_1-V_2, V_2-A_2) (Fig. 6). The fast pathway had a longer refractory period than the slow pathway, and conduction failed at a V_1–V_2 interval of 250 msec (the effective refractory period of the fast pathway); then the slow pathway assumed retrograde conduction. Supraventricular tachycardia was induced whenever the slow pathway was utilized for V-A conduction (Fig. 7, A and B). Figure 7 reveals that tachycardia was not induced at a coupling interval of 260 msec and an S_2-A_2 interval of 120 msec (fast pathway conduction) (panel A) but was induced at a coupling interval of 250 msec and an S_2-A_2 interval of 210 msec (slow pathway) (panel B). Intracardiac mapping during tachycardia demonstrated that retrograde atrial activation occurred first in the low septal right atrium, preceding that in the low lateral right atrium, left atrium and high right atrium by 25, 25 and 30 msec, respectively (Fig. 8, A to D). During tachycardia the ratio of anterograde to retrograde conduction (Ae-H/H-Ae ratio) was less than 1 (Fig. 8D). Tachycardia could be terminated by ventricular extrasystoles. Reinstatement of tachycardia followed progressive shortening of the sinus cycle length.

Discussion

Surface electrocardiographic identification of fast-slow A-V nodal reentrant tachycardia: Atrioventricular nodal reentry as an underlying mechanism for supraventricular tachycardia has been postulated on the basis of critical analyses of the surface electrocardiogram.[23–27] Electrophysiologic stimulation techniques have confirmed that dual A-V nodal pathways frequently provide the underlying mechanism for reentrant tachycardia in adults[5,6,8–12,14–16] and children.[1,3] The most commonly reported A-V nodal reentry circuit involves a slow pathway for anterograde

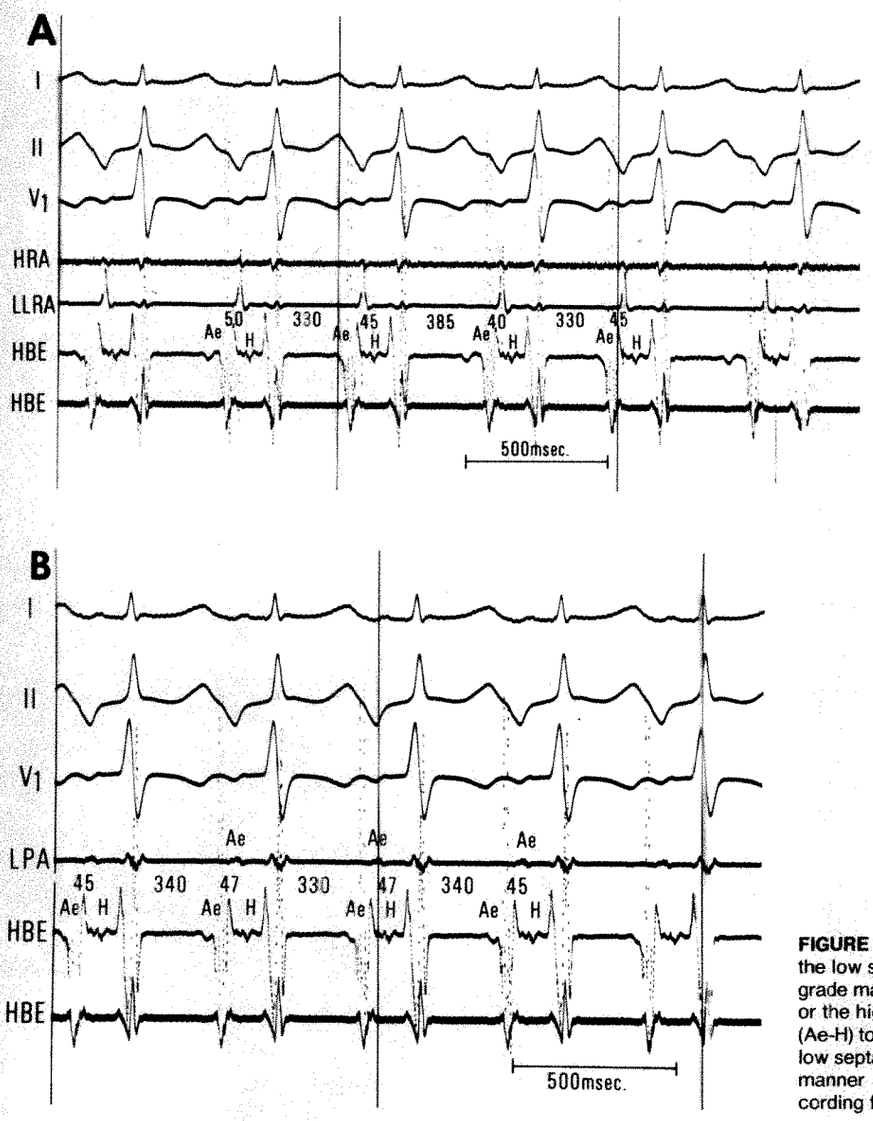


FIGURE 4. Case 1. Atrial mapping during tachycardia. **A**, the low septal right atrium (HBE) is depolarized in retrograde manner before the low lateral right atrium (LLRA) or the high right atrium (HRA). The ratio of anterograde (Ae-H) to retrograde (H-Ae) conduction is 45/330. **B**, the low septal right atrium (HBE) is depolarized in retrograde manner before the left atrium, as indicated in the recording from the left pulmonary artery (LPA).

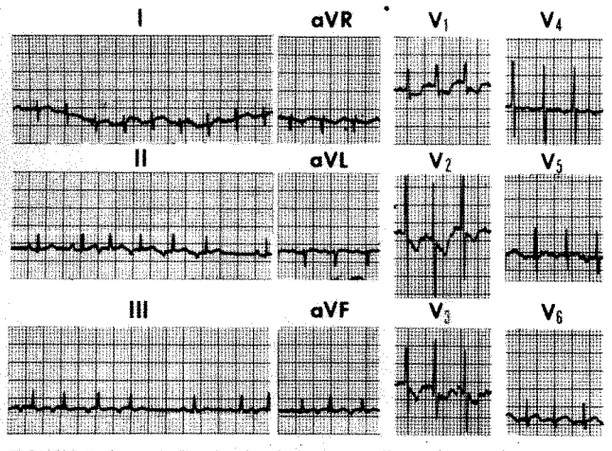


FIGURE 5. Case 2. Twelve lead electrocardiogram reveals supraventricular tachycardia (rate 188/min). The P waves are inverted in leads II, III, and aVF. The P-R/R-P ratio is 0.5. Lead II demonstrates spontaneous induction of tachycardia (beats 1 and 2 are sinus beats); beat 3 is the first beat of the tachycardia and initiates a retrograde Wenkebach period that terminates the tachycardia (beat 6) by block in the slow retrograde pathway. Lead III shows the same phenomenon (beats 1 through 4); the tachycardia terminates with retrograde block; spontaneous tachycardia recurs after two sinus beats (beats 5 and 6).

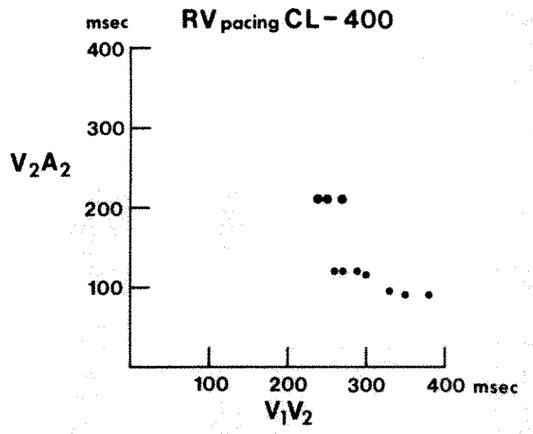


FIGURE 6. Case 2. V_1-V_2 V_2-A_2 conduction curve during right ventricular (RV) pacing at a cycle length (CL) of 400 msec. The **small black circles** represent conduction over the fast pathway (retrograde conduction time [V_2-A_2] between 80 and 120 msec). The curve becomes discontinuous at a V_1-V_2 interval of 260 msec when there is a sudden increase in V-A conduction time to 210 msec (the slow pathway represented by **large black circles**). Tachycardia was always induced when the slow pathway was utilized for retrograde conduction.

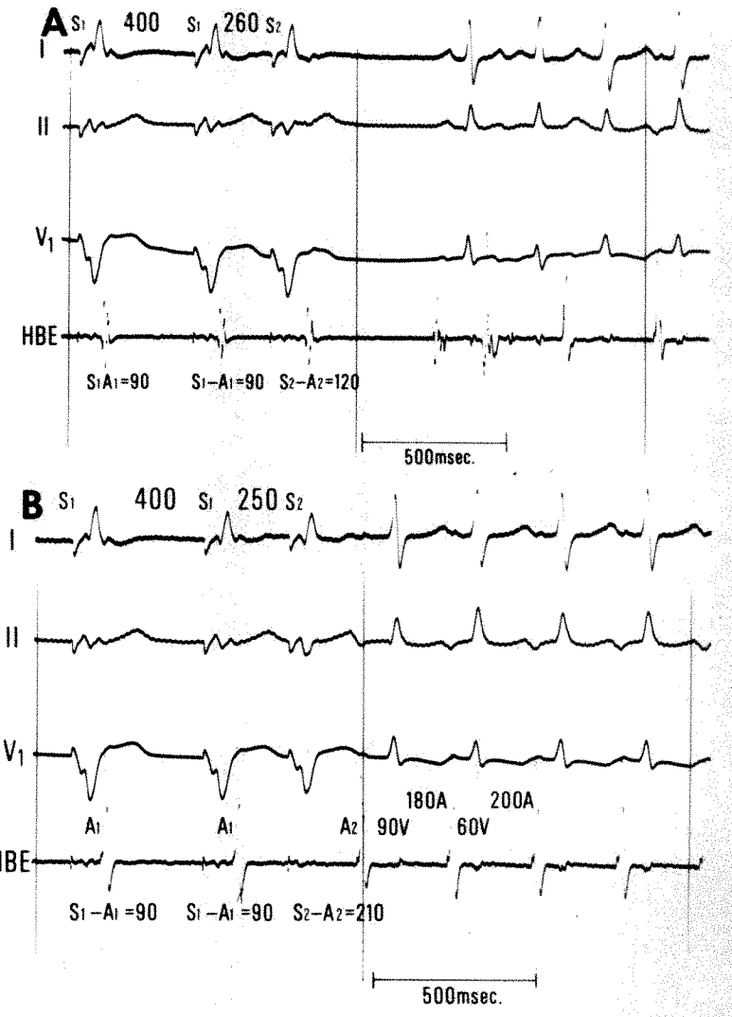


FIGURE 7. Case 2. **A,** ventricular extrastimulus (S_1-S_2) delivered at 260 msec with a right ventricular pacing cycle length of 400 msec (S_1-S_1). Tachycardia is not induced. The V-A conduction time (S_1-A_1) with basic pacing is 90 msec; the conduction time (S_2-A_2) with the ventricular extrastimulus is 120 msec (the fast pathway). HBE = His bundle electrogram. **B,** ventricular extrastimulus (S_1-S_2) delivered at 250 msec produces sustained tachycardia. The V-A conduction time with basic pacing (S_1-A_1) is 90 msec; the V-A conduction time with the ventricular extrastimulus (S_2-A_2) is 210 msec (the slow pathway).

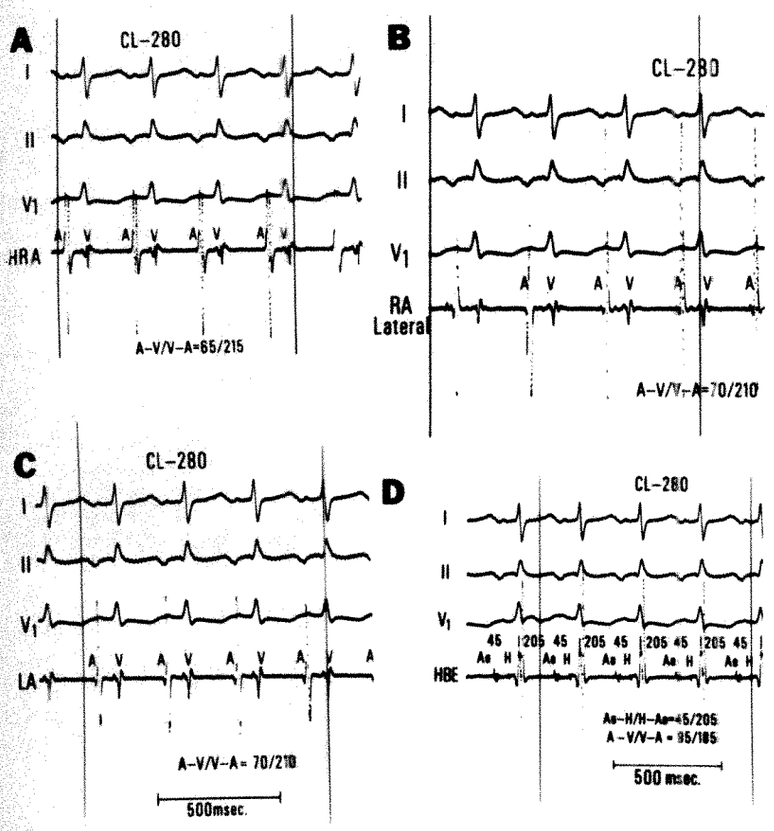


FIGURE 8. Case 2. Atrial mapping during tachycardia with a cycle length (CL) of 280 msec. **A**, retrograde depolarization of the high right atrium (HRA) occurs late with a conduction time (V-A) of 215 msec. **B**, retrograde depolarization of the lateral right atrium (RA Lateral) occurs slightly earlier, with a conduction time (V-A) of 210 msec. **C**, retrograde depolarization of the left atrium (LA) occurs at the same time as that of the lateral right atrium, with a conduction time (V-A) of 210 msec. **D**, retrograde depolarization of the low septal right atrium (HBE) occurs earliest with a conduction time (V-A) of 185 msec. The ratio of anterograde (Ae-H) to retrograde (H-Ae) conduction time is 45/205.

conduction and a fast pathway for retrograde conduction.[8,11,12,16] The surface electrocardiogram may not be helpful in the common type of reentrant tachycardia because the P waves may be obscured by the QRS complex. This occurs because the fast conducting pathway conducts the impulse in retrograde fashion to the atrium at nearly the same time that the slow conducting pathway transmits the impulse in anterograde fashion to the ventricle. In the uncommon form of A-V nodal reentrant tachycardia a fast pathway is utilized for anterograde conduction and a slow pathway for retrograde conduction.[10,11,13–16] In this situation, the surface electrocardiogram is most helpful. Because retrograde atrial activation occurs by way of the slow pathway the P wave is inscribed far from the QRS complex, making it easily discernible and resulting in a long R-P interval; anterograde ventricular activation occurs by way of the fast pathway, accounting for a short P-R interval. Therefore a P-R/R-P ratio of less than 1 is supporting evidence for the fast-slow form of reentrant tachycardia and is helpful in distinguishing the latter from a supraventricular tachycardia involving a concealed accessory pathway for retrograde (fast) conduction, because in the latter the P-R/R-P ratio is greater than 1.[16]

Although a fast-slow form of A-V nodal reentrant tachycardia has not previously been documented in pediatric patients, it is probably a common mechanism underlying the resistant form of supraventricular tachycardia in children. Coumel et al.[26,27] suggested that such a mechanism, although uncommon in adults, was common in persistent tachycardia in children. In their report[26] on eight children, they stressed the constant electrocardiographic features of a superior axis of the P wave and a P-R/R-P ratio of less than 1 during tachycardia. Other authors[28,29] have commented on this pattern in children. Keane et al.[29] reported 16 cases of resistent tachycardia and found a superior P wave axis in 69 percent and a short P-R and long R-P interval. As early as 1922 Gallavardin[30] reported three cases of supraventricular tachycardia that he distinguished from the usual form; in one of these three cases the P axis was superior and the P-R/R-P ratio was less than 1. He and his co-workers described similar cases in subsequent reports.[31,32]

Continuous versus discontinuous V-A conduction curves: One may fail to demonstrate discontinuous A-V or V-A conduction curves in the presence of dual pathways when the refractory period of one of the pathways is very long or when there is unidirectional block.[6,33–35] In the fast-slow form of reentrant tachycardia one may demonstrate, with atrial extrastimulation, exclusive conduction over the fast pathway when the slow pathway has a longer refractory period than the

fast pathway.[16] In a similar manner, one may demonstrate with ventricular extrastimulation a continuous retrograde V-A conduction curve in which the fast pathway has a longer refractory period than the slow pathway and V-A conduction proceeds only over the slow pathway.[16] The latter curve was demonstrated in our Case 1. At a critical coupling interval the ventricular extrastimulus (V_2), is conducted in retrograde manner over the slow pathway and blocked in retrograde manner in the fast pathway. This allows reentry of the impulse in an anterograde fashion over the fast pathway and permits institution of tachycardia. Although the study in Case 1 was limited by a single left atrial recording site (left pulmonary artery), a left-sided accessory bypass appears unlikely because the depolarization at that site was considerably later than depolarization of the low septal right atrium (Fig. 4B); additionally, the A-V conduction curve demonstrated nodal conduction characteristics (Fig. 2). One may demonstrate a discontinuous V-A conduction curve during programmed ventricular stimulation when the fast pathway is utilized at longer and the slow pathway at shorter cycle lengths.[14,16] The latter curve was obtained in our Case 2. The fast pathway (retrograde direction) was blocked at a critical cycle length, V-A conduction proceeded through the slow pathway, allowing anterograde conduction over the fast pathway and thereby establishing the circuit for reentrant tachycardia. The findings in our two cases do not exclude the possibility of an accessory nodal-ventricular fiber (Mahaim) connecting the slow A-V nodal pathway with the ventricles.

Thus, an underlying mechanism for incessant tachycardia of childhood has been documented electrophysiologically as a fast-slow form of A-V nodal reentry. The electrophysiologic findings correlate with a specific electrocardiographic pattern consisting of a superior axis of the P wave and a P-R/R-P ratio of less than 1 during tachycardia.

Acknowledgment

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Left Ventricular Radius to Wall Thickness Ratio

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Left ventricular relative wall thickness, expressed as the ratio of end-diastolic radius to wall thickness (R/Th ratio), has a constant relation with left ventricular systolic pressure in children and adults with a normal heart, subjects with physiologic forms of cardiac hypertrophy (athletes) and patients with compensated chronic left ventricular volume overload (chronic aortic regurgitation). Greatly increased values for the radius/thickness ratio, suggesting inadequate hypertrophy, indicate a poor prognosis in patients with chronic aortic regurgitation and in those with congestive cardiomyopathy; decreased values for this ratio are found in patients with hypertrophic cardiomyopathy (inappropriate hypertrophy) and in patients with compensated aortic stenosis (appropriate hypertrophy). In patients with compensated aortic stenosis, echocardiographic measurement of the left ventricular end-diastolic radius/wall thickness ratio has been used to estimate left ventricular systolic pressure. Measurement of left ventricular relative wall thickness appears to provide diagnostic and prognostic data in patients with a broad variety of cardiac disorders.

Left ventricular "relative wall thickness," expressed as the end-diastolic volume/mass (V/M) or end-diastolic chamber radius/wall thickness (R/Th) ratio, has provided important diagnostic and prognostic information in patients with heart disease.[1–5] It has also provided insight into some of the differences among the various forms of myocardial hypertrophy. The basis for these observations rests in the Laplace relation, which states that left ventricular wall stress (S) is directly proportional to intracavitary pressure (P) and chamber radius (R) and is inversely proportional to wall thickness (Th): $S = P \cdot R/Th$. Systolic wall stress is normal and a constant relation between systolic pressure and the ratio of chamber radius to wall thickness (R/Th) is maintained in the normal growing child.[1] This constant relation between pressure and the chamber radius/wall thickness ratio is also maintained in trained athletes[6] and in normal pregnant women[7] (both of whom may have increased left ventricular chamber size) and in many patients with compensated valvular heart disease.[5,8] When sufficient hypertrophy does not develop in response to a hemodynamic load and normal systolic wall stress is not maintained, the radius/thickness ratio may be increased. As will be seen, measurement of the *end-diastolic* ratio provides information that can be useful in analyzing a broad variety of cardiac disorders. The purpose of this review is to discuss the diagnostic and prognostic importance of the left ventricular relative wall thickness. A detailed analysis of the physiologic basis of these observations was presented in recent reviews by Ford[1] and Mirsky.[9]

Left ventricular chamber volume, wall thickness and myocardial mass have generally been measured in man using cardiac catheterization and

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angiographic techniques, but in recent years echocardiography has provided a noninvasive, safe and inexpensive method of measuring left ventricular dimension and wall thickness. Most of the information presented herein involves the chamber radius/thickness ratio determined from M mode echocardiographic measurements.

Relation Between Ventricular Radius, Thickness and Pressure

Physiologic hypertrophy: The degree to which left ventricular muscle mass is appropriate for the chamber size is reflected in the inverse relation between the left ventricular end-diastolic radius/thickness (R/Th) ratio and left ventricular systolic pressure; this relation is shown diagrammatically in Figure 1. The area labeled "normal LV" encompasses not only the normal heart (of children as well as adults),[1] but also the enlarged heart of the marathon runner[6] and the volume-loaded heart of the normal pregnant woman.[7] Thus, the increased left ventricular muscle mass seen in these subjects can be considered a normal or *physiologic form of cardiac hypertrophy*. The hearts of many patients with chronic compensated left ventricular volume overload (that is, chronic aortic regurgitation) would also be included in this normal area[5,8]; in such patients, left ventricular hypertrophy must be considered appropriate and compensatory.

Appropriate versus inappropriate and inadequate hypertrophy: Systolic blood pressure is elevated and the radius/thickness ratio is low in patients with *appropriate* left ventricular hypertrophy (secondary to aortic valve stenosis) (Fig. 1); such ventricles appear to have moved to a low portion of the compensated radius/thickness ratio versus pressure relation. Most patients with nonobstructive hypertrophic cardiomyopathy also have a low ratio with a normal left ventricular systolic pressure; this (downward) shift from the normal radius/thickness ratio versus pressure relation implies *inappropriate* hypertrophy. Patients with chronic congestive cardiomyopathy may show a high radius/thickness ratio and a normal left ventricular systolic pressure; in this instance, the ratio versus pressure coordinate is shifted upward and to the right, implying *inadequate* hypertrophy of the ventricle (insufficient muscle mass relative to chamber volume).

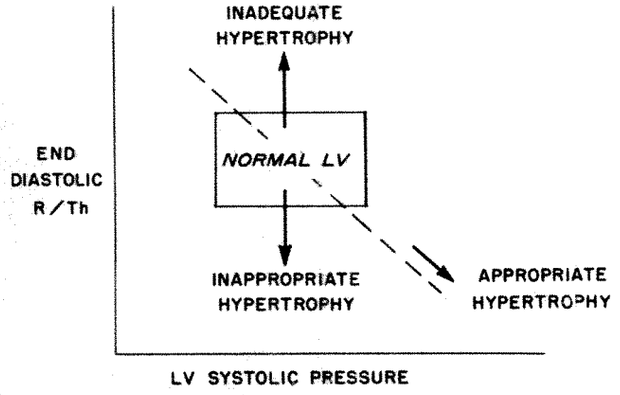


FIGURE 1. Diagrammatic representation of the relation between left ventricular (LV) end-diastolic radius/wall thickness (R/Th) ratio and systolic pressure. This relation reflects the degree to which left ventricular muscle mass is appropriate or adequate for chamber size. In patients with compensated aortic stenosis (appropriate hypertrophy), echocardiographic measurement of the radius/thickness ratio has been used to estimate left ventricular systolic pressure.

These three situations exemplify long-term changes in the radius/thickness ratio, but certain acute changes in the ratio can also be examined within the framework of Figure 1. For example, aortic valve replacement for aortic stenosis may normalize left ventricular systolic pressure, but in the early postoperative period a low radius/thickness ratio persists; in this manner, the ventricle undergoes acute conversion from *appropriate* to *inappropriate* hypertrophy, and only after the regression of myocardial hypertrophy will the ratio return to normal. Also, in patients with acute left ventricular failure and dilatation or in those with acute aortic insufficiency, the radius/thickness ratio would be expected to show an upward and rightward shift. Although this would ordinarily suggest *inadequate* hypertrophy, such a conclusion might be open to question because there would not have been sufficient time for a hypertrophic response. These examples of acute changes in the radius/thickness ratio must be interpreted in the light of the acute hemodynamic alterations, and under most circumstances this analysis is most useful in the presence of *chronic* alterations in relative wall thickness.

In summary, coordinates that lie above the physiologic or compensated radius/thickness ratio versus pressure relation indicate *inadequate* hypertrophy (and elevated systolic wall stress), and coordinates that lie below this relation indicate *inappropriate* hypertrophy (and low wall stress). Coordinates that are on the normal line or relation (normal wall stress) indicate a *physiologic* form of hypertrophy, which occurs in athletes, or *appropriate* hypertrophy, which occurs in compensated aortic valve disease. The normal inverse relation between end-diastolic radius/thickness ratio (R/Th) and systolic pressure is approximated by the equation of Ford[1] (R/Th = 1/0.0027P, where P is left ventricular systolic pressure); in normotensive subjects, this ratio averages 3.0 ± 0.7 (mean ± 2 standard deviations).[5]

The Athlete's Heart

Cardiomegaly, gallop rhythms and electrocardiographic abnormalities are often present in the trained athlete. Although such findings often indicate cardiac disease in the sedentary population, it is now apparent that repetitive dynamic exercise results in a physiologic form of cardiac hypertrophy. Roeske et al.[6] reported echocardiographic measurements of left ventricular dimensions and performance in a group of professional athletes. On the basis of increased right and left ventricular dimensions as well as increased left ventricular wall thickness (compared with that of control subjects matched for age and body size), they concluded that

cardiac hypertrophy was present in these athletes; left ventricular end-diastolic dimension and posterior wall thickness averaged 53.7 ± 1.3 and 11.1 ± 0.6 mm, respectively, in the athletes and 49.9 ± 0.7 and 9.8 ± 0.3 mm in the control group. In these athletes, left ventricular function (as judged from the extent and velocity of circumferential fiber shortening) was not significantly different from that of the control subjects. Despite the presence of left ventricular enlargement and of electrocardiographic, vectorcardiographic and phonocardiographic findings that are generally considered abnormal, normal systolic performance was taken as evidence that the athletes were "free of organic cardiovascular disease." If the left ventricular end-diastolic radius/thickness ratio is estimated from the average ventricular dimension/thickness data reported by Roeske et al.,[6] the values for the group of athletes (2.6) and the control group (2.4) are similar. Thus, despite significant left ventricular enlargement in the athletes, the (radius/thickness) (or the volume/mass) ratio is essentially normal. This normal relation between left ventricular chamber size and myocardial mass can be considered evidence for a physiologic (normal) form of cardiac hypertrophy in trained athletes.

Congestive Cardiomyopathy

In a study of 36 patients with cardiomyopathy and depressed ejection fraction, Feild et al.[2] observed that the degree of relative hypertrophy, expressed as the mass/volume ratio, influenced survival. Left ventricular chamber size, function and mass were determined angiographically; end-diastolic volume ranged from 104 to 347 ml/m^2 body surface area, and the systolic ejection fraction ranged from 0.09 to 0.41. In these patients, the systolic ejection fraction and the mass/volume ratio were then related to the subsequent clinical course.

The postcatheterization survival rates for these 36 patients are shown in Figure 2. Data from the 15 patients with an ejection fraction greater than 0.20 are compared with the data from the 21 patients with an ejection fraction smaller than 0.20; each of these two groups are further classified according to the mass/volume ratio. Although the survival rate appears to be related to the ejection fraction, it also appears to be lower when ventricular hypertrophy is inadequate (mass/volume ratio 0.90 or less) than when it is appropriate for the degree of left ventricular dilatation (mass/volume ratio 0.90 or more). When the mass/volume ratio was related to the precatheterization duration of dyspnea and to the survival of patients with a recent onset of dyspnea, a higher mass/volume ratio again correlated with greater degrees of compensation and with longer survival. Feild et al. concluded that both systolic performance and the degree of hypertrophy are important in determining survival in patients with congestive cardiomyopathy, and they further suggested that ". . .the degree of hypertrophy influenced survival, at least in part, independent of the level of ventricular function as expressed by ejection fraction."

Chronic Aortic Regurgitation

The preoperative end-diastolic radius/thickness ratio has recently been proposed[5] as a prognostic index in

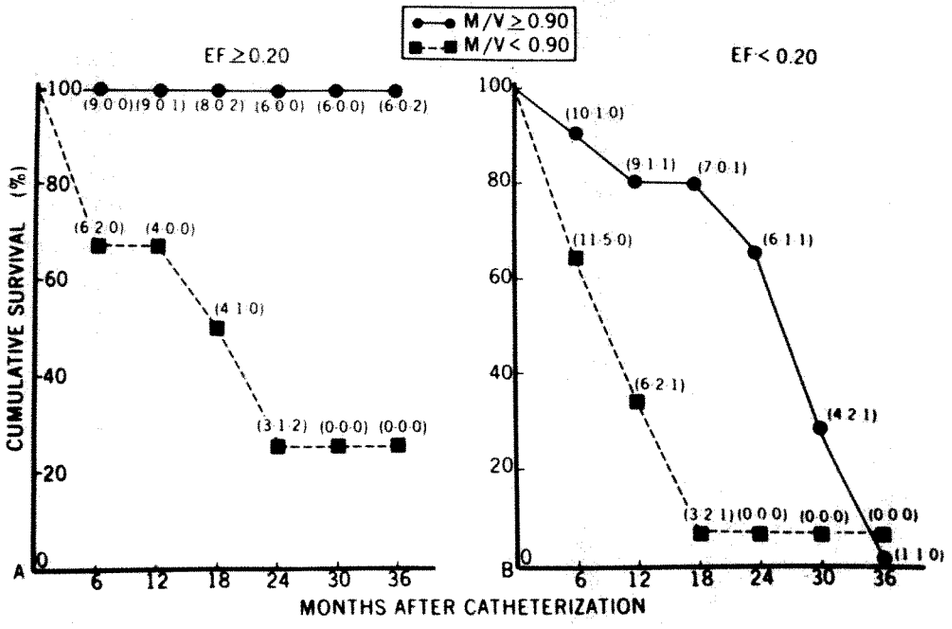


FIGURE 2. Survival rates after cardiac catheterization for 36 patients with congestive cardiomyopathy reported on by Feild et al.[2] The patients were grouped according to the mass/volume (M/V) ratio and the systolic ejection fraction (EF). The three figures in parentheses at each data point indicate (from left to right) the number of patients alive at the beginning of the time interval, the number who died during the interval, and the number who had not yet reached the next interval. A low M/V ratio indicates a poor prognosis in both ejection fraction groups. (Reprinted from Feild et al.[2] with permission of the American Heart Association, Inc.)

patients undergoing aortic valve replacement for chronic aortic regurgitation. In a group of 19 patients with chronic aortic regurgitation followed up with serial postoperative echocardiographic left ventricular studies, 15 showed a significant reduction in end-diastolic dimension or volume and a significant regression of myocardial hypertrophy (satisfactory postoperative result); 4 additional patients failed to show a reduction in left ventricular volume or mass after aortic valve replacement. When preoperative data were examined in a search for indexes that might predict the outcome of aortic valve replacement, it became apparent that those patients with a much higher than normal preoperative radius/thickness ratio did not have an optimal surgical result. In the 15 patients with a satisfactory postoperative result, the preoperative radius/thickness ratio was 3.9 or less; the 4 with a preoperative ratio of 4.0 or more failed to show a significant reduction in left ventricular volume or muscle mass.[5]

The preoperative data (radius/thickness ratio and left ventricular systolic pressure) from these 19 patients with chronic aortic regurgitation are shown in Figure 3; the normal range for radius/thickness ratio versus systolic pressure is shown by the broken line, and data from 12 patients with mild aortic regurgitation are shown for reference. The curvilinear line relating radius/thickness ratio to left ventricular systolic pressure is derived from Ford's equation.[1] Such normalization for pressure is essential in the interpretation of these data. Preoperative data from the patients with a satisfactory result lie slightly above and to the right of normal; the data from the patients with persistent postoperative left ventricular enlargement lie even further up and to the right. This marked deviation from the normal radius/thickness ratio versus pressure relation reflects a failure of hypertrophy to match the chronic volume load imposed on the ventricle (inadequate hypertrophy). It thus appears that the relative degree of left ventricular hypertrophy has important prognostic value in patients with chronic aortic regurgitation as well as in those with congestive cardiomyopathy.

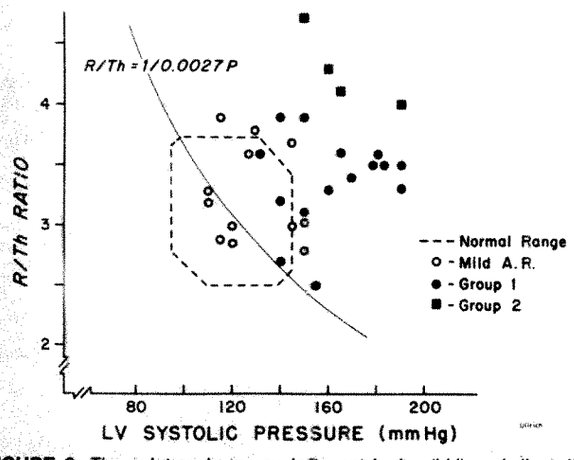


FIGURE 3. The relation between left ventricular (LV) end diastolic raidus/wall thickness (R/Th) ratio and systolic pressure (P) in 31 patients with chronic aortic regurgitation (A. R.). The area enclosed by the **broken line** defines the range of normal values. The data from 12 patients with mild aortic regurgitation **(open circles)** lie within or near the normal range. The curvilinear line and the regression equation are from the study of Ford.[1] Preoperative data from 19 patients who underwent aortic valve replacement are shown: 15 (Group 1, **closed circles**) experienced a satisfactory postoperative result and 4 (Group 2, **closed squares**) a less than satisfactory result. See text for details.

Aortic Stenosis

Estimation of left ventricular pressure from radius/thickness ratio: In patients with aortic stenosis, the noninvasive estimation of left ventricular systolic pressure can be an important clinical application of the echocardiographic measurement of the radius/thickness ratio. Because left ventricular systolic wall stress remains normal in patients with compensated aortic stenosis (appropriate hypertrophy), Bennett et al.[3] reasoned that *systolic* relative wall thickness should be an index of systolic wall stress. In these studies, systolic relative wall thickness was taken as the ratio between end-systolic wall thickness and end-systolic cavity dimension (systolic thickness/dimension ratio). Their rationale was based on knowledge that wall stress (force/unit cross-sectional area of muscle) is directly proportional to pressure and radius and is inversely proportional to wall thickness; if systolic wall stress is normal, then pressure should be predictable from measurements of radius and wall thickness. Using echocardiography in 63 patients with and without aortic valve disease, Bennett et al. measured systolic thickness/dimension (Th/D) ratio and found that left ventricular peak systolic pressure could be estimated from the formula: left ventricular pressure = 225 Th/D. Peak systolic aortic valve gradients compared well with the gradients measured at the time of cardiac catheterization. Bennett et al. were aware that left ventricular peak systolic pressure did not occur at the same time as the measured systolic thickness/dimension ratio, but this theoretical limitation did not preclude their use of the latter ratio as a predictor of left ventricular systolic pressure.

On the basis of observations of Grossman et al.[8] (that the thickness/radius ratios at end-diastole and at peak systolic stress are quite similar), Aziz et al.[4] were able to estimate left ventricular peak systolic pressure from the *end-diastolic* thickness-radius (Th/R) ratio. The use of the end-diastolic Th/R ratio as an index of peak systolic stress appealed to them, "because left ventricular peak wall stress occurs in early systole in close temporal relation to the left ventricular peak systolic pressure at a point in the cardiac cycle when no significant left ventricular wall thickening has occurred and when the Th/R ratio is approximately equal to the end-diastolic Th/R ratio." Left ventricular systolic pressure was determined from the formula: pressure = 6 + 298 (Th/R), where Th/R is the ratio between diastolic wall thickness and the chamber radius. As did Bennett et al., Aziz et al. emphasized that this noninvasive method of estimating left ventricular peak systolic pressure was useful only in the absence of myocardial decompensation. Although a statistically significant correlation exists between left ventricular relative wall thickness and systolic pressure, in the indi-

vidual patient the predictive value of this technique is limited, and it is likely that further refinements will be necessary before it can be used extensively as a clinical tool.[10,11]

End-diastolic versus end-systolic thickness-dimension data: Several other groups[12–14] have successfully used similar methods, and all are in agreement that the ratio of wall thickness to chamber size at end-systole can be used to estimate left ventricular systolic pressure. Although the use of end-diastolic thickness/dimension data has not been tested extensively, there are several reasons to believe that *end-diastolic* data should be at least as useful as *end-systolic* data. First, there are the theoretical arguments that peak systolic stress occurs near end-diastole and that end-diastolic thickness/radius ratio is very similar to the ratio at peak stress.[8] Second, end-diastolic dimension and wall thickness measurements appear to be more reproducible than end-systolic measurements.[15] Third, if fractional shortening of the circumference or diameter is normal and the fractional increase in wall thickness is normal, then the end-systolic thickness/radius ratio must be related to the end-diastolic ratio; thus, when left ventricular function is normal, there should be little difference between the conclusions derived from one method or the other. This is evident when one uses the combined data of Bennett and Aziz and co-workers[3,4] (Fig. 4). The linear correlation coefficient between *end-systolic* radius/thickness ratio and peak systolic pressure ($r = 0.69$) is similar to the correlation coefficient between *end-diastolic* radius/thickness ratio and peak systolic pressure ($r = 0.75$).

Conclusions

The data reviewed herein emphasize the potential clinical utility of the radius/thickness ratio in a broad variety of cardiac conditions. In the physiologic cardiac hypertrophy seen in the trained athlete and in the appropriate hypertrophy seen in the patient with compensated chronic aortic regurgitation, both left ventricular chamber size and wall thickness are increased so that the ratio remains normal. An increased radius/thickness ratio (one that clearly exceeds the normal value of 3.0 ± 0.7) indicates a poor prognosis in patients with chronic aortic regurgitation, and a similar conclusion is warranted in patients with congestive cardiomyopathy. In compensated aortic stenosis, the left ventricular wall thickness is increased without an associated increase in chamber size, and thus the ratio is decreased. The inverse relation between radius/thickness ratio and systolic pressure (Fig. 1) allows the noninvasive estimation of left ventricular systolic pressure in groups of patients with aortic stenosis and appropriate left ventricular hypertrophy; such estimates appear theoretically sound and are statistically valid, but unfortunately the predictive value in any individual patient appears limited.[10]

Limitations of the radius/thickness ratio as a clinical tool: These probably originate in problems with the accuracy and reproducibility of the echocardiographic measurements.[16] We and others[17] have previously concluded that small (less than 2 mm) changes in the echocardiographic left ventricular dimension do not represent clinically significant changes

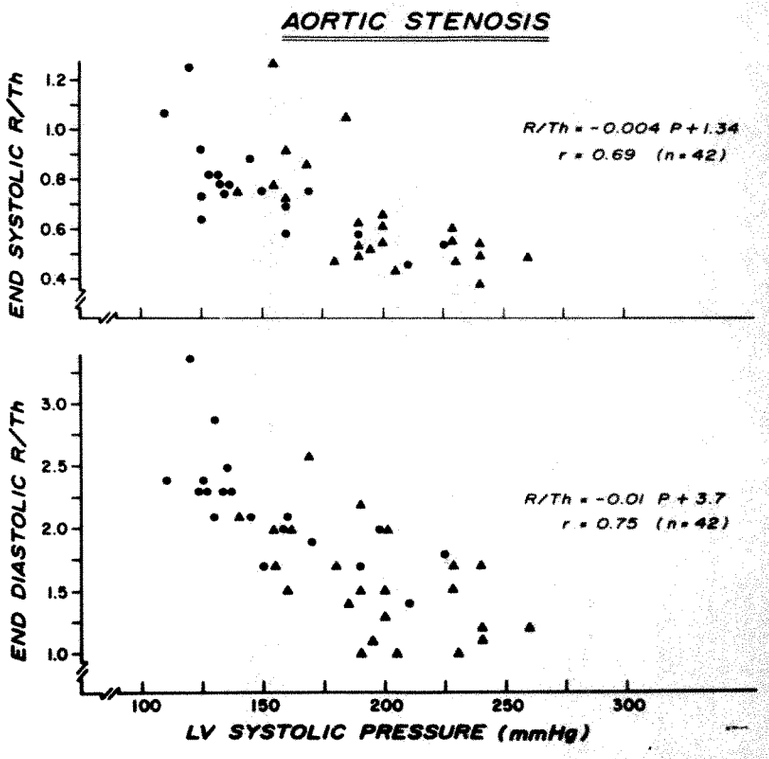


FIGURE 4. The left ventricular (LV) *end-systolic* radius/wall thickness (R/Th) ratio (**upper panel**) and *end-diastolic* R/Th ratio (**lower panel**) are plotted against left ventricular systolic pressure in 42 patients with aortic stenosis. These data, derived from echocardiographic and cardiac catheterization measurements, were generously supplied by Bennett et al.[3] (**triangles**) and by Aziz et al.[4] (**circles**). In patients with compensated aortic stenosis, it appears that left ventricular systolic pressure may be estimated from either the end-diastolic or the end-systolic radius/thickness ratio. See text for details.

in ventricular volume. In the calculation of left ventricular volume, the results of measurement errors are magnified because volume is a cube function of the radius. Measurement errors can also significantly influence radius/thickness ratio, even in the absence of a cube function. For example, if a patient with chronic aortic regurgitation has a 7 cm end-diastolic dimension and a wall thickness of 1 cm, the R/Th ratio is 3.5; a 2 mm measurement error in end-diastolic dimension (1 mm error in radius) at a constant wall thickness of 1 mm yields an R/Th ratio of 3.4 to 3.6. However, if the 1 mm radius error is associated with a (directionally opposite) error in the wall thickness measurement, the R/Th value is influenced to a much greater degree; if radius is measured as 3.4 cm and the wall thickness as 1.1 cm, the R/Th ratio is 3.1, and if the radius is measured as 3.6 cm and the wall thickness as 0.9 cm, the R/Th ratio is 4.0. Thus, in this example, relatively small measurement errors can significantly influence the R/Th ratio.

Similarly, if a patient with aortic stenosis has an end-diastolic dimension of 4 cm (radius = 2 cm) and a wall thickness of 1 cm, the estimated left ventricular systolic pressure would be 155 ± 13 mm Hg.[4] However, a 1 mm additive error (as in the example given of aortic regurgitation) results in a left ventricular systolic pressure ranging from 134 ± 13 mm Hg (for a thickness/radius ratio of 0.9/2.1) to 179 ± 13 mm Hg (for a ratio of 1.1/1.9). Thus, in this example, a 1 mm additive measurement error results in approximately a 20 mm Hg difference in left ventricular systolic pressure. Small measurement errors potentially limit the extensive use of the ratio in clinical cardiology; our present methods of measuring left ventricular radius and wall thickness need improvement.

Other potential clinical applications: In addition to the studies summarized in this review, other data indicating several other potential applications of the radius/thickness ratio also deserve critical investigation. Preliminary data suggest that the ratio has value in the search for the origins of altered left ventricular diastolic compliance[9,18]; continued research in this area is indicated. The radius/thickness ratio might also be a key to the progression or regression of myocardial hypertrophy in serial studies of patients under treatment for arterial hypertension.[19] Furthermore, the extent to which mixed valve disease alters the radius/thickness ratio is not known, and the prognostic value of the ratio in mitral valve disease has not been defined. These potentially fertile areas of future research remain to be explored, and the studies reviewed herein require confirmation and refinement.

Acknowledgment

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Introduction

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Since the initial description of myocardial infarction and the demonstration that occluding clots in the coronary circulation are associated with infarction and sudden death, the mechanism of thrombus formation and methods to control clotting have been of interest to cardiologists and other physicians who treat patients with heart disease. The discovery that many patients with myocardial infarction die of pulmonary emboli added impetus to the performance of clinical trials of anticoagulation in patients admitted to the hospital with myocardial infarction. The initial studies demonstrated an impressive beneficial effect of anticoagulation, and very soon the use of heparin and warfarin, or its derivatives, was as routine in the management of the patient with a heart attack as was the use of oxygen, sedation and bed rest. As further well controlled studies were carried out, the initial overwhelming enthusiasm began to abate. The less impressive results with regard to the effect on death rate may have been due to better study design. However, earlier ambulation and other methods to decrease the incidence of venostasis and deep vein thrombophlebitis also may have played a part in decreasing the difference in mortality between patients receiving anticoagulant therapy and control subjects. Throughout the late 1950's and into the 1960's numerous debates were conducted in the medical journals and at national meetings as to whether the benefit of anticoagulation outweighed the potential of bleeding complications. Cardiology rounds in hospitals throughout the country frequently discussed when and how to use anticoagulation in patients with myocardial infarction. "Definitive" study after "definitive" study appeared that purported to solve this clinical dilemma.

With the large incidence of thrombophlebitis and pulmonary embolism that often follows myocardial infarction, the management of thrombophlebitis not necessarily associated with infarction has also become the province of cardiologists in many hospitals. Over the years this development has led to the creation of more sophisticated methods for diagnosing and managing phlebitis and of many techniques, including small dose heparin therapy, for preventing its occurrence.

The use of antifibrin anticoagulation has been of value in decreasing the incidence of thrombophlebitis and systemic emboli but has not been effective in preventing the progression or recurrence of myocardial infarction. Recently, attention has been turned to blood platelets and their role in the origin of myocardial infarction. Blood platelets have been known for some time to play the initiating role in the formation of clots in the arterial system, maintaining the integrity of the vascular system and preventing bleeding. Inappropriate platelet aggregation in the arterial system could theoretically lead to occlusion of a narrowed area in a coronary artery and result in myocardial infarction. The availability of a wide variety of drugs already in use for other indications that also have inhibiting effects on platelet aggregation have led to trials of antiplatelet drugs in patients with coronary artery disease. The report in the winter of 1978 of a beneficial effect of sulfinpyrazone in preventing death in patients with myocardial infarction has brought this newer method of affecting the clotting mechanism to the attention of cardiologists and physicians who manage patients with coronary artery disease. It has also excited interest in the lay public through various media reports. The theoretical suggestion that platelets may play a part in the origin of the arteriosclerotic plaque has led to further interest in antiplatelet therapy.

The three papers in this Seminar review the current thinking on the use of anticoagulation in the management of coronary artery disease and thrombophlebitis and discuss the available data linking blood platelets with coronary artery disease and with myocardial infarction.

In their paper, Frishman and Ribner review the current status of anticoagulation in the management of myocardial infarction. They discuss the value of anti-

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coagulation in the prevention of deep vein thrombosis and pulmonary embolism in patients with infarction. They also cover the value of anticoagulation in preventing peripheral and cerebral arterial emboli, further complications that occasionally change a benign post-infarction course into a catastrophic one. The complications of anticoagulant therapy and the various forms of anticoagulation are presented and the use of small dose heparin therapy after myocardial infarction is discussed. Recommendations are presented as to which patients should receive anticoagulant therapy, for how long and using what regimens.

New techniques for diagnosis and prevention of thrombophlebitis are reviewed by Sasahara, Sharma and Paresi. In recent years more precise methods for detecting early venous thrombosis have been developed. Sasahara et al. discuss in depth the relatively new technique of impedance plethysmography, which appears to be a sensitive and relatively specific method for noninvasively documenting venous occlusion and for confirming the diagnosis of pulmonary embolism. Sasahara et al. discuss the data available on the benefit of small dose heparin therapy, dextran and antiplatelet aggregating agents used for this purpose. Physical measures such as elevation of the legs, use of elastic stockings and early ambulation remain to be fully proved as effective preventative measures. Intermittent calf muscle compression with the external pneumatic boot has recently received attention as an effective measure in many patients for prevention of venous thrombosis. The authors review the data supporting the use of this device, especially in patients who are not candidates for small dose heparin therapy.

The final paper in the Seminar presents the data leading to the concept that blood platelets play a role in coronary artery disease. Evidence is available that platelet aggregates forming inappropriately in the vasculature of the heart can cause ischemic damage. Platelet aggregates can stimulate spasm and may be an initiating factor in the origin of the arteriosclerotic lesion. Most of the coronary risk factors have been found to be associated with platelet function abnormalities. Findings such as these have been the stimulus for the performance of a number of clinical studies that have explored the value of various platelet aggregation inhibiting drugs in the prevention of infarction or death in patients with coronary artery disease. The results of the studies of clofibrate, aspirin and the recent report of the use of sulfinpyrazone for this purpose are presented and discussed. Although all of the data on the value of the antiplatelet drugs is not yet formulated, on the basis of what is available, recommendations as to the use of these agents are presented.

Modification of the clotting mechanism has now become a recognized form of therapy. Although the "definitive" study with regard to the use of antifibrin drugs has not yet been performed, the large accumulation of data justifies the reasonable use of these agents. Antiplatelet therapy in coronary disease is only in its early stages now and further reports are needed that will define its theoretical benefit. It is our hope that this short symposium will serve to clarify the role of therapy aimed at modification of blood clotting in cardiovascular disease and to provide the background material with which the treating cardiologist can evaluate further developments in this field.

Role of Blood Platelets in Coronary Artery Disease

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Over the past decade, research in blood platelet physiology has led to the suggestion that platelets play an important part in the pathogenesis and complications of coronary artery disease. Occlusive intravascular platelet aggregates have been shown to cause ischemic myocardial damage in the experimental animal and to be present in some patients who die suddenly. The interplay between endothelial damage and platelet aggregation has been implicated in the etiology of atherosclerosis. Products released from platelets during aggregation may cause arterial spasm. Patients with overt ischemic heart disease and with the risk factors associated with coronary artery disease have been found to have abnormally reactive platelets.

Clinical studies of drugs that inhibit platelet aggregation have been reported to show a beneficial effect in preventing cardiac deaths or myocardial infarction; other studies have been negative or shown only a trend toward benefit. This report reviews the theoretical and experimental basis for the platelet hypothesis and the current data on the use of antiplatelet drugs in patients with coronary disease.

In recent years, blood platelets and the possible role they play in the etiology and natural history of coronary artery disease have attracted increasing attention among researchers and cardiologists. The reasons for this interest have included theoretical considerations concerning platelet physiology and function, epidemiologic findings relating coronary risk factors with abnormalities in platelet function and clinical findings of an increased incidence of abnormal platelet function among patients with coronary artery disease. These data have been the stimulus for several clinical drug studies, one of which, the sulfinpyrazone study, has excited dramatic reports in the lay press of a breakthrough in preventing myocardial infarction. It is the purpose of this paper to review current thinking on the relation of platelets to coronary artery disease and to present the current status of antiplatelet aggregation therapy in the management of coronary artery disease.

Blood Platelet Physiology[1]

Blood platelets act as the first defense of the body against hemorrhage. They circulate in the bloodstream as elliptical flat discs. When stimulated, usually by a break in the endothelial lining of a blood vessel, they are attracted to the defect, they round up, develop pseudopods, become sticky and adhere to the abnormal area, forming a plug that repairs the defect and reestablishes the continuity of the smooth endothelial surface. The platelet is a complex structure. Although lacking a nucleus it contains numerous organelles including granules, a microtubular system, a metabolically active membrane and contractile proteins.

After the platelets adhere to an area of damage, the reversible first stage of platelet aggregation, the adhering platelets undergo the release reaction associated with the second stage of aggregation, and additional platelets are attracted to the defect and join the aggregate, enlarging it. During this phase the substances within the granules are extruded through the microtubular system out of the platelets and into the surrounding area. The substances released include adenosine diphosphate (ADP), catecholamines, serotonin, enzymes and prostaglandins such

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as thromboxane A2. These substances serve to stabilize the platelet aggregate in addition to stimulating additional platelets to aggregate. Thromboplastins are also released during this phase of aggregation and, if a sufficient number of platelets have been involved, the cascade system that results in the conversion of fibrinogen to fibrin is activated, and a typical clot develops. If the defect is large, a large amount of fibrin is formed, red cells become enmeshed in the fibrin strands and a recognizable red clot results.

Usually, it is collagen exposed to the bloodstream when there is a break in the endothelial surface that attracts platelets and stimulates them to adhere and to aggregate, but other stimuli can initiate the aggregation process. These include circulating catecholamines, ADP, prostaglandins, immune complexes and fatty acids. Excessive turbulence can also cause platelets to aggregate.

Platelets and Ischemic Heart Disease

Currently, platelets are thought to participate in clinical coronary disease in two ways, in association with acute myocardial infarction and sudden death and by participation in the development of atherosclerosis.

Platelet aggregation and coronary occlusion: Theoretically, a platelet aggregate, stimulated by circulating catecholamines, immune complexes or excessive turbulence, might form inappropriately within the circulating blood. Such a platelet aggregate might lodge in an area of narrowing of an artery, close it off and lead to ischemia of the area fed by that artery. If such an aggregate were to occlude a narrowed coronary artery, myocardial infarction, possibly associated with a ventricular arrhythmia and sudden death, might occur. A platelet aggregate stimulated to form and cover a break in the endothelial lining of an artery might break off from the area of formation, travel in the bloodstream to a coronary artery and, lodging in an area of narrowing, then occlude it. Moreover, it is possible that rupture of the endothelial lining over an atherosclerotic plaque within a coronary artery might stimulate the formation, in situ, of a platelet aggregate that might grow to occlude the remaining lumen over the plaque.

The evidence that such events might indeed occur comes from several sources. First, it has been shown that platelet aggregates forming within the circulatory system can lead to myocardial damage in the experimental animal. Jorgensen et al.[2] infused ADP directly into the coronary arteries of pigs. All nine animals that died within 5 minutes of the onset of infusion had platelet aggregates in their coronary arteries. Among the 20 animals that lived beyond 2 hours, 16 were found to have gross infarcts and 17 had microscopic infarcts on histologic examination. This was a significantly greater incidence of infarction than among 17 pigs given intracoronary infusions of adenosine monophosphate (AMP), which does not stimulate platelet aggregation. In the two latter groups there was no difference in the incidence of arterial platelet aggregates found, suggesting that platelet aggregates might form, do their damage, disaggregate and disappear before pathologic study.

In the early 1970's we[3] demonstrated that the intravenous infusion of catecholamines in dogs caused intravascular aggregation of platelets in the small vessels of the heart. Electron microscopy revealed platelet aggregates in the myocardial vessels of dogs infused for 4 hours with norepinephrine. The diffuse cardiac necrosis[4] known for years to occur after epinephrine infusion was found to be prevented by pretreatment with aspirin,[5] dipyridamole[5] or clofibrate,[6] drugs that have little in common other than inhibition of platelet aggregation. These findings suggest that the diffuse myocardial fibrosis seen after extensive catecholamine therapy or in patients with pheochromocytoma is at least partially due to intravascular platelet aggregation.

In 1976 Folts et al.[7] demonstrated that spontaneously occurring platelet aggregates could cause occlusion of an experimentally narrowed section of a canine coronary artery. They showed that flow through a critically narrowed coronary artery was phasic, with periods of no flow alternating with near normal flow at rest. These changes were associated with sudden reductions in pressure distal to the narrowing that would suddenly revert to near normal pressure, suggesting that the compromised lumen was alternately being totally occluded and then opened. On sectioning the area of narrowing during the time of complete occlusion, they found a pure platelet aggregate plugging the lumen. They postulated that platelet aggregates were intermittently occluding the stenotic section of the coronary artery and that these plugs would break up and be flushed through the area of narrowing, intermittently opening the obstruction. They postulated that such events might not be uncommon in a human being with atherosclerotic heart disease, and that angina at rest or serious ventricular arrhythmias and sudden death might occur during the periods of occlusion. In further studies, these authors[8] demonstrated that these phasic changes in coronary blood flow through a narrowed artery could be abolished by pretreating with drugs that inhibit platelet aggregation.

The extent of infarction after total occlusion of a coronary artery might also be affected by secondary platelet aggregates. Moschos et al.[9] demonstrated that in the periphery of an infarct created by total experimental occlusion of a coronary artery, there was an increased concentration of platelets sequestered in the myocardial vasculature. In animals pretreated with aspirin these aggregates were not found and the resulting area of infarction was smaller. They postulated that the extent of an infarct might be influenced by the degree of platelet aggregation in the borders of the area of infarction.

Fatal arrhythmias and sudden death: Pathologic findings in patients who have died suddenly have supported the concept that an occluding platelet aggregate might be the event that triggers a fatal arrhythmia.[10] Haerem[11] reported a significantly greater incidence of

platelet microthrombi in patients with coronary artery disease who died suddenly than in patients who died from other causes. Forty-seven percent of 47 patients who died suddenly were found to have acute microthrombi in their coronary vessels compared with 15 percent of 13 patients who did not die suddenly and had no coronary artery disease.

Platelets and coronary spasm in myocardial infarction: Recently Oliva and Breckenridge[12] presented data on patients with acute myocardial infarction that might implicate platelets as playing an important part in the acute event. They subjected 15 patients to coronary arteriography within a few hours after the onset of acute myocardial infarction and infused nitroglycerin directly into the occluded vessel that appeared to have led to the infarction. In almost half of the patients the nitroglycerin infusion caused the vessel to dilate and the area of occlusion to open and become less than total. These findings suggest that spasm may play a role in the acute occlusion that leads to infarction. The strongest vasoconstrictor produced endogenously is thromboxane A2,[13] a prostaglandin that is released from the platelet as it undergoes the second stage of aggregation. It is conceivable that a platelet aggregate might lodge in an area of narrowing in a coronary artery, release thromboxane A2, and cause spasm of the artery, stabilizing the occlusion and maintaining the total blockage. Such an occlusion would be expected to open partially if the spasm were relieved. Although not yet proved, the findings of Oliva and Breckenridge can be interpreted to support the concept that inappropriate intravascular platelet aggregation may be the inciting event that leads to infarction.

Data from our laboratory[14] have supported the findings of Oliva and Breckenridge. Of 106 patients with anterior myocardial infarction on electrocardiography and definite anteroapical dyskinesia or akinesia on left ventricular angiography, 23 patients were found on coronary arteriography to have a narrowed but patent left anterior descending coronary artery. It is possible that in these patients recanalization occurred or that a less than total occlusion caused infarction. More probably, however, a platelet aggregate, may have first totally occluded the stenotic area for sufficient time to result in infarction and then disbanded and passed downstream, opening the occluded area or, alternatively, spasm played a role and, with release of the local spasm, the vessel regained partial patency. The report of Oliva and Breckenridge[12] suggests that the latter two possibilities with the possible involvement of platelets might provide the more reasonable explanation.

Platelets and Atherosclerosis

Investigations into the biology of the arterial vessel wall have led to the concept that platelets may also play an important role in the initiation of atherosclerosis.[15] Studies on the endothelial lining and vascular smooth muscle cells have suggested that injury to the vascular endothelium stimulates the proliferation of smooth muscle cells and their migration into the intima where they actively absorb lipid and secrete fibrin, elastin and tissue matrix, the components that can become the typical atherosclerotic complex lesion. The trigger of this response of vascular smooth muscle cells appears to be a substance released from platelets as they undergo the second stage of platelet aggregation.

Platelets and endothelial trauma: The evidence for this theory comes from various sources. Experimental injury to the vascular endothelium by mechanical disruption with a balloon catheter scraped across its surface,[16] by chronic exposure to high levels of homocystine[17] or cholesterol in the blood[15] or by immune injury[18] results in large areas of denudation of endothelial cells on the intimal surface. These areas are promptly covered by aggregated platelets. Within a few days after injury, smooth muscle cells have been demonstrated to be migrating from the muscularis layer into the intimal subendothelial parts of the vessel wall. In 1 to 3 months large numbers of these cells are found in the intima and have been demonstrated to form collagen fibrils, proteoglycans, mucopolysaccharides and elastin fibers. It may take 9 months for the endothelium to regenerate completely. If this occurs and further injury does not again stimulate the smooth muscle cells, the changes in the muscle cells in the intima regress and the vessel wall returns almost to normal. However, if the injury is repetitive or there are large amounts of lipid in the serum, these vessel abnormalities may not regress and instead may degenerate into typical atherosclerotic lesions.[15]

Platelets and proliferative smooth muscle response: The pivotal role of platelets in this sequence of events has been suggested by several factors: (1) Endothelial trauma induced in these ways is usually associated with a shortening of platelet survival time. (2) Inhibition of platelet function by drugs that block platelet aggregation[19] or by making the experiment animal thrombocytopenic prevent the smooth muscle cell response. (3) It has been shown in vitro that there is a substance released from platelets as they aggregate that will stimulate and support proliferation of smooth muscle cells.[15] The character of this substance is not yet clear, but it appears similar to a fibroblast growth factor extracted from the pituitary gland. It is possible that the platelet does not produce this substance but just carries it to be released at sites of endothelial damage.[15] The source of the material, whether produced by the megakaryocte or elsewhere, remains conjectural. Other substances, especially low density lipoproteins, appear to play a supportive role in this proliferative smooth muscle cell response, perhaps providing the raw materials for the cells to use as they proliferate and produce extracell matrix and collagen.

Role of risk factors: This theory of the origin of atherosclerosis is very attractive in that it is compatible with what is known about the risk factors for atherosclerosis. Endothelial injury induced by the mechanical hemodynamic stress of hypertension, the catecholamine response to cigarette smoking, the effect of serum carbon monoxide from cigarette smoke, the chronic expo-

sure to high cholesterol levels and possible vessel abnormalities associated with diabetes may be the common characteristic of these risk factors that leads to atherosclerosis by means of the platelet aggregation that such injury induces.

Historical background: Although this theory is relatively new, the consideration that thrombosis may play a role in the development of atherosclerosis may be traced to Von Rokitansky[20] in the 1850's. He believed that vascular mural clots degenerated into atherosclerotic plaques. Duguid[21] in the 1940's demonstrated pathologic evidence that mural thrombi could acquire an endothelial covering, supporting Von Rokitansky's concepts. Mustard's laboratory[22] has produced data suggesting that platelet clots themselves could damage vascular endothelium through enzymes released during aggregation and that such damage to the endothelial lining might make the surface more permeable to transudation of lipids into the intimal layer of the vessel wall, thereby bringing into accord the ultrafiltration theory of atherosclerosis with the thrombogenic concept. Thus evidence is accumulating that platelets and their function as the initiator of intraarterial thrombosis and as the first responders to endothelial injury may be a significant factor in the etiology of atherosclerosis.

Epidemiologic Data Linking Platelets With Coronary Artery Disease

In addition to the theoretical considerations concerning the platelet as a factor in the pathogenesis of clinical ischemic heart disease, numerous studies have demonstrated a large incidence of abnormally reactive platelets in patients with coronary artery disease. Adhesiveness of platelets was reported to be abnormal in patients with clinical coronary disease.[23–27] Platelet aggregation studied with the aggregometer was shown to be significantly enhanced[28–31] and platelet survival time was shown to be significantly shortened[26,30,32] among patients with clinical coronary disease. Hampton and Gorlin,[33] using platelet electrophoretic techniques, also noted significant abnormalities in patients with coronary disease. Although all reports have not agreed with these findings, the majority of investigations have demonstrated a correlation between coronary artery disease and more responsive platelets regardless of the specific platelet function test utilized. The finding that patients with coronary disease have more reactive platelets can be interpreted either as evidence that these patients are more prone to mural vascular thrombi and occlusive vascular thrombi, and thereby to atherosclerosis and acute myocardial infarction, or as evidence that atherosclerosis is already present and the recurring stimuli to platelets caused by the areas of narrowing in the vascular tree may be manifested by more reactive platelets.

Risk Factors and Platelet Function

The effects of the presence of known coronary risk factors on platelet function have been extensively investigated. Patients with hyperlipidemias, especially hypercholesterolemia, have been shown to have more sensitive platelets.[34] Carvalho et al.[35] found that the platelets of patients with type II hyperlipidemia responded to significantly lower concentrations of epinephrine and collagen in the aggregometer than did platelets of control patients. A diet high in saturated fats leads to increased platelet aggregability, and even a high fat meal will cause acutely enhanced platelet reactivity.[25,36] Smoking cigarettes[37,38] increases the activity of platelets acutely, and cigarette smokers have a shortened platelet survival time. Asymptomatic patients with a family history of, or relatives with, coronary artery disease have been shown to have a high incidence rate of platelet function abnormalities.[33] Patients with diabetes have significantly more easily stimulated platelets than do control subjects.[36,39] In a series of studies[40,41] performed on normal house officers we recently showed that emotional stress has a potent effect on platelet function.

The observation that all these risk factors are associated with platelet abnormalities suggests that the risk factors may affect the vasculature through their platelet effects, and it indirectly supports the concept that platelets may play an etiologic role in clinical coronary artery disease. However, these findings can only be considered circumstantial evidence; the platelet abnormalities noted may be only coincidental events in the development of coronary disease rather than a causal factor.

Clinical Pharmacologic Studies

The experimental evidence and theoretical considerations linking platelet function with coronary artery disease have led to the logical conclusion that inhibition of platelet function might prevent acute myocardial infarction and the development or progression of coronary atherosclerosis. The availability of a large number of drugs[42] that are used primarily for other purposes but that also have potent antiplatelet activity has led to a number of drug trials and reports. The drugs most studied have been aspirin, sulfinpyrazone, clofibrate and dipyridamole.

Aspirin

Aspirin is a potent platelet aggregation inhibitor.[43] It appears to work by inhibiting the production of prostaglandins.[44] It blocks the second phase of platelet aggregation and the release reaction.

Aspirin in the prevention of myocardial infarction: The use of aspirin in the prevention of myocardial infarction is not new. In the early 1950's, Craven[45] suggested a trial of aspirin in middle-aged men. Some years later he[46] reported the results in 8,000 men who had taken one or two aspirin tablets daily for about 6 years. There were no instances of myocardial infarction in this treated group during the period of the uncontrolled study. In 1951, an autopsy study[47] of 131 patients followed up in an arthritis clinic and presumably taking large doses of aspirin over a prolonged period of time revealed only 4 percent to have died with myocardial infarction and only 2 percent with stroke, an incidence rate far below that expected for a similar population.

Over the subsequent years a number of reports[48,49] from arthritis clinics confirmed or denied this paucity of myocardial infarction among patients with arthritis.

More recently the results of two prospective studies on aspirin for prevention of infarction and death have been reported.[50,51] Beginning in February 1971, the British group of Elwood et al.[50] randomized 1,239 men with history of recent myocardial infarction to treatment with either aspirin, 300 mg/day, or placebo and followed them up for a few months to 2 1/2 years. Analysis of the cumulative death rates showed a consistently lower mortality rate among the group receiving aspirin (7.6 versus 10.1 percent at 1 year, 9.0 versus 13.2 percent at 18 months, 12.2 versus 18.5 percent at 2 years). However, at no time did the difference achieve statistical significance. Separating the patients according to age did not improve the statistical significance, but classifying the patients according to the interval from infarction to entrance into the trial gave a somewhat more interesting result. Among the patients entering the study less than 6 weeks after infarction, 7.8 percent of the aspirin-treated men died compared with 13.2 percent of the control subjects. By applying the chi-square formula, chi-square equals 5.27, suggesting a statistically significant difference beyond the 0.025 level. Elwood et al. were reluctant to report any significant difference in this group because most of the patients came from one area, and it was not clear if this was an interval effect or a geographic aberration. In view of the positive findings in the sulfinpyrazone group in which all patients were entered into the trial within 35 days of infarction, these results in the study of Elwood et al. might be important. However, the investigators considered their findings "inconclusive," although a trend toward a benefit for aspirin was clearly identified.

The second reported prospective therapeutic trial of aspirin is the Coronary Drug Project Aspirin Trial.[51] The Coronary Drug Project was designed to determine if any of a number of cholesterol-reducing drugs would decrease the mortality among patients who had survived at least one myocardial infarction. Three of the drug regimens being tested, D-thyroxine and large and small dose estrogen, were clearly found to be of no benefit and possibly harmful within a few years after recruitment was completed. Testing of these drugs was stopped. After at least 6 months on no active medication, 1,529 of these well worked-up patients were randomized to treatment with aspirin, 5 grains three times daily, or a placebo, and subsequently followed-up for 10 to 28 months. The total mortality rate in the aspirin-treated group was 5.8 percent, approximately 30 percent below the 8.3 percent rate of the placebo group, although the difference was not statistically significant. Using various end points other than mortality such as myocardial infarction or other coronary events and various combinations of end points consistently showed a trend favoring aspirin, but no statistical significance was achieved. Unfortunately, funding was not available to continue the trial. Criticisms about the value of this study include the fact that most of the participants had had their infarction more than 3 years before entry into the aspirin trial and had been taking other medications for long periods before entry into the trial. Nevertheless, there was a trend, although not of statistical significance, toward benefit of aspirin therapy.

Data from the Boston Collaborative Drug Surveillance Group has supported the use of aspirin as preventive treatment for myocardial infarction.[52] These investigators interviewed patients in the hospital as to the drugs they had been taking before admission and correlated the diagnoses on discharge with the patterns of drug use and other habits. Two studies were simultaneously reported. In the first study 0.9 percent of 325 patients with myocardial infarction reported long-term use of aspirin whereas 4.9 percent of 3,807 patients with other diagnoses gave such a history ($P < 0.003$). Among 451 patients with myocardial infarction in the second study, 3.5 percent had a history of regular use of aspirin compared with 7.0 percent of 10,091 patients with other diagnoses ($P < 0.03$). Multivariate analysis did not diminish this negative association between regular use of aspirin and myocardial infarction, suggesting that aspirin may be protective against myocardial infarction.

Another epidemiologic study, carried out under the auspices of the American Cancer Society,[53] did not find any beneficial effect of aspirin in coronary artery disease. A 6 year follow-up study of more than 1 million men and women who answered a questionnaire concerning diet, habits and drugs revealed that among the approximately 43,000 men and 29,000 women who died with a diagnosis of myocardial infarction there was no significant difference in the number of persons who never used aspirin or used it often when compared with control subjects who had not had coronary disease. Analysis of the data according to age or sex did not affect these negative conclusions.

Implications: As yet no prospective studies have demonstrated a statistically significant benefit of aspirin in coronary artery disease. The two large studies reported both suggest a trend, and the Boston Collaborative Drug study has been reported as positive. We are currently awaiting the results of the Aspirin-Myocardial Infarction Study sponsored by the National Institutes of Health and the aspirin-dypridamole (Persantin®) study sponsored by Boehringer Ingelheim. Both studies are in the process of following up large numbers of patients who have survived a myocardial infarction and have been randomized to treatment with aspirin or placebo (Aspirin-Myocardial Infarction Study) (AMIS) or to treatment with dipyridamole, dipyridamole and aspirin, or placebo groups (Persantin-Aspirin Reinfarction Study) (Paris). Results are expected in the next 1 to 2 years.

Sulfinpyrazone

The drug that has caught the interest of many in the past year has been sulfinpyrazone (Anturane®).[54] Sulfinpyrazone, an antigout drug that was developed during research on butazolidin, has been known to have potent platelet-inhibiting effects for some years.[55] It has

been shown to be useful in maintaining patency of arteriovenous shunts used for hemodialysis[56] and to have a beneficial effect in patients with transient cerebral ischemic attacks.[57] In 1972, Blakely and Gent[58] presented the results of a prospective double-blind trial of sulfinpyrazone, 600 mg/day, in 291 elderly institutionalized men. They followed up the patients for 4 years and found a statistically significant increase in survival among the patients with a previous history of atherosclerosis who had been treated with sulfinpyrazone in comparison with patients treated with a placebo, especially among those who died of vascular causes. The numbers were too small to separate those who died of myocardial infarction for separate analysis.

Multicenter randomized study: In 1975, a large multicenter therapeutic trial[54] of sulfinpyrazone was organized to determine if the drug had any value in preventing death during the first 1 or 2 years after myocardial infarction. Data were accumulated on 1,475 patients who were randomized to treatment with either placebo or sulfinpyrazone, 200 mg four times daily, starting 25 to 35 days after a documented acute myocardial infarction. By the time recruiting was completed in July 1977, it was apparent that there was a statistically significant benefit with sulfinpyrazone and the results of the study were reported. The appearance of the data in the *New England Journal of Medicine*[54] in February 1978 immediately stimulated headlines in the *New York Times*, the *Wall Street Journal* and other prestigious papers throughout the world, acclaiming that an important breakthrough in the therapy of heart attack had been achieved. Of the 69 deaths in the study group, 68 were cardiac; 44 occurred in the placebo group and 24 in the patients treated with sulfinpyrazone, a difference in cardiac mortality that was significant ($P = 0.18$). The biggest difference was among those who died suddenly, with 29 of the placebo group and 13 of the treated group having a sudden death during the study period ($P = 0.015$). The cardiac death rate corrected for exposure time (mean 8.4 months) was 9.5 percent for the placebo group and 4.9 percent for the treated group, a death rate reduction among the treated group of 48.5 percent. The annual sudden death rate was 6.3 percent in the placebo group and 2.7 percent in the treated group, a reduction of 57 percent associated with treatment with sulfinpyrazone. However, the number of deaths due to myocardial infarction—12 in the placebo group and 9 in the treated group—was not statistically significantly different. The occurrence of rehospitalization for myocardial infarction and cardiac arrhythmias tended to be lower among the treated patients but the difference was not statistically significant, whereas the frequency of admission for heart failure or angina tended to be greater among the treated patients.

Although it was originally planned to continue the study until all patients had been followed up for at least 1 year, because ongoing analysis of mortality demonstrated a statistically significant reduction in deaths among the sulfinpyrazone-treated patients the results were reported after a mean of 8.4 months follow-up. The investigators planned to inform the study patients of the results and hoped to gain the cooperation of a sufficient number of these patients to continue the study with sufficient numbers to generate further significant follow-up data. Further reports from the investigational team are anxiously awaited.

Limitations of study: A number of criticisms were generated by the report. First, more patients in the placebo than in the treated group appeared to have had arrhythmias during infarction ($P < 0.05$), and, although the difference was not statistically significant, there tended to be more patients with previous myocardial infarction, bundle branch block, angina, diabetes and claudication among the placebo group. This has raised the question whether, by multivariate analysis,[59] the placebo group might not prove to be significantly sicker than the treated group, and the results therefore spurious. Second, the finding that the major beneficial effect of the drug was in the prevention of sudden death rather than the prevention of further myocardial infarction suggests that sulfinpyrazone may be acting primarily as an antiarrhythmic drug, possibly through an effect on prostaglandins,[60] and that results may have little relation to the drug's effect on platelets. Third, the mode of reevaluation of the data during the study has been criticized as possibly making a less significant difference appear more important than is justified.[61] Furthermore, it remains unclear if the benefit noted in this short follow-up period will continue to remain significant as the patients are followed up further, and if the small incidence of side effects will also continue as the patients receive the drug for more prolonged periods.

It is expected that many of these criticisms will be more adequately resolved when the final report of the group is presented. Recent comments from members of the investigating team at meetings have suggested that a large number of participants in the study are continuing in the protocol and that more data should be expected. A study similar to this American-Canadian study is currently underway in Italy[62]; confirmatory data will be of great value.

Other Antiplatelet Drugs

Clofibrate: This drug, used primarily for the lowering of serum lipid levels, is also an effective platelet aggregation inhibitor.[63,64] Several studies of its efficacy in preventing death in patients with coronary artery disease have been reported in recent years.[65,66] A cooperative study performed in Newcastle-on-Tyne[65] demonstrated a significant decrease in the incidence of death in patients with evidence of angina or myocardial infarction, or both, who were treated with clofibrate and followed up over a 5 year period. The beneficial effect of the drug in 497 randomly assigned patients did not appear to correlate with a specific effect of the drug on lipid levels. A similar study performed by the Research Committee of the Scottish Society of Physicians[67] found similar results in patients followed up for 6 years, although they noted a significant decrease in death rate only in their patients who had angina with or without a previous infarction and not in those who had had a previous infarction but not angina. Again the beneficial

effect of the drug did not appear to be related to a lipid-lowering effect.

A randomized study performed among United Airlines' personnel[66] demonstrated a significant decrease in the occurrence of myocardial infarction among men initially free of evidence of coronary disease and among men who had a history of myocardial infarction or angina, or both, who were randomized to treatment with clofibrate. These findings were not related to any lipid-lowering effect noted. The lack of correlation of benefit with serum lipid effects suggests that another mechanism, such as the platelet aggregation inhibition known to occur with the drug, might be operant. However, the Coronary Drug Project study of clofibrate did not confirm the findings in these three studies.[68] There was no significant benefit with regard to mortality noted among the patients with a history of at least one myocardial infarction who had been randomized to treatment with clofibrate. The reason for this disparity remains unclear but is probably related to patient selection. The positive British studies included patients with angina alone, suggesting that possibly clofibrate is of greater benefit when begun earlier in the course of the disease.

A cooperative Edinburgh-Budapest-Prague Study of clofibrate in the prevention of ischemic heart disease in middle-aged men without manifest heart disease has been reported.[69] Approximately 30,000 men were screened and those with serum cholesterol levels in the top third of the cohort were separated into two groups. Approximately 5,000 men were randomly assigned to treatment with clofibrate (Group I) and 5,000 to receipt of placebo (Group II). These men were further compared with about 5,000 men randomly selected from those with cholesterol levels in the lower one third of the cohort who received placebo (Group III). The average follow-up period was 5.3 years. Cholesterol levels were decreased by approximately 9 percent below the initial cholesterol level in the treated group (Group I). Men in this group had 25 percent fewer nonfatal infarctions ($P < 0.05$) than men in the high cholesterol-placebo group (Group II) but significantly more than men in the low cholesterol-placebo group (Group III) ($P < 0.01$). The incidence rate of fatal infarction and sudden death did not differ significantly between Groups I and II but were significantly lower in Group III. These findings, coupled with further analysis of the data, led to the suggestion "... that most of the reduction of nonfatal myocardial infarction in the clofibrate treated group is associated with reduction of cholesterol concentrations." However, multivariate analysis revealed "... that treatment (with clofibrate) may have some additional effect beyond that of cholesterol reduction ..." although "... the excess effect is not itself significant."

A number of disquieting results appeared in this study. First, there was a significantly higher death rate among the treated patients ($P < 0.05$) than among the untreated high cholesterol patients, with a trend toward a greater incidence of deaths from cancer (although rates were similar to those in Group III and in the local population). Second, there was a greater incidence of disease of the liver, gall bladder and intestines and of mortality due to disease of these organs in the clofibrate-treated group than in either the high or the low cholesterol group treated with placebo.

These recent data support the conclusions of the earlier British studies and the United Airlines Study that clofibrate is effective in decreasing coronary artery disease morbidity although they disagree with previous findings by demonstrating that this effect is largely related to, rather than independent of, a cholesterol-lowering effect. Whether the platelet effects of clofibrate were of importance in this cooperative study is conjectural.

Beta adrenergic blocking drugs: These agents have also been demonstrated to have a significant platelet-inhibiting effect.[37,70] In a prospective study of practolol,[71] the investigators found a significant decrease in cardiac mortality and in combined nonfatal myocardial infarction and death (but not in infarction alone). Although these results are probably related to the antiarrhythmic and antiischemic effects of the drug, the antiplatelet effect may play a role. Practolol is not available, but it would be expected that propranolol would have a similar effect. A randomized study of propranolol in patients after infarction, sponsored by the National Institutes of Health is underway; the results will be of great interest.

Dipyridamole: This is another drug with antiplatelet activity[72] that has elicited interest among cardiologists. Although studies suggesting its efficacy in the prevention of emboli associated with prosthetic valves have been reported,[73] its value in the management of coronary artery disease has not yet been documented. In a current prospective trial (Persantin Aspirin Reinfarction Study, PARIS) patients with a documented infarction are being randomized to treatment with either dipyridamole, dipyridamole and aspirin, or placebo and are being prospectively followed up. Results are expected to be reported within the next 2 to 3 years.

Negative Aspects of Antiplatelet Therapy

Two other aspects of the use of antiplatelet aggregation drugs must be taken into account when use of these agents is being considered. The first is related to a theoretical negative effect of these agents and the second to possible side effects.

Role of Prostaglandins

Recently a new prostaglandin has been discovered, prostacyclin I2.[74] This agent appears to have properties almost directly opposite to those of thromboxane A2. Thus, instead of stimulating platelets to aggregate and blood vessels to constrict, prostacyclin I2 (PG I2) prevents or reverses platelet aggregation and relaxes and dilates blood vessels. Instead of being found in the platelet, it is synthesized in the walls of arteries and veins and is located primarily in the vascular endothelium. Teleologically, its function is probably to inhibit the formation of occlusive platelet aggregates and to maintain the patency of the vascular system. One reason that platelets do not normally adhere to the endothelial lining of vessels may be that endoperoxides released from the platelets may be converted to PG I2 by the

appropriate endothelial enzyme (prostacyclin synthetase) and adhesion and aggregation are inhibited. If there is a break in the endothelial lining, the loss of this newly formed prostacyclin and its attendant aggregation inhibition may be the reason that platelets aggregate on areas of damage and theoretically contribute to the formation of an atherosclerotic plaque. In addition, the presence of a plaque may inhibit the formation of the prostacyclin and thus favor the formation of a clot at the site of the atherosclerotic lesion that occludes the vessel or contributes to further growth of the plaque.

Prostacyclin I2 versus thromboxane A2 inhibition: The reason that the existence of prostacyclin I2 might complicate pharmacologic antiplatelet therapy is that at least some of these drugs, especially aspirin and drugs of the nonsteroidal antiinflammatory type (including possibly sulfinpyrazone), act through inhibition of cyclooxygenase. Natural synthesis of the prostaglandins is thought to proceed from arachidonic acid to the cyclic peroxides using cyclooxygenase as the catalytic enzyme. These cyclic peroxides are the precursors of the other prostaglandins, being specifically converted in the presence of thromboxane synthetase in the platelet to thromboxane A2 and, in the presence of prostacyclin synthetase in the blood vessel lining, to prostacyclin I2. Thus the process that leads to the synthesis of both thromboxane A2, the platelet-aggregating agent and vasoconstrictor, and prostacyclin I2, the inhibitor of platelet aggregation and vasodilator, is repressed by these platelet-inhibiting drugs. Experiments with various blood levels of aspirin have not been successful in finding a dosage of aspirin that will inhibit production of thromboxane A2 without also inhibiting coronary vasodilation,[75] which is thought to be related to the production of PG I2. Theoretically then it is not known whether on balance the benefit of inhibition of thromboxane A2 outweighs the liability of inhibiting the production of prostacyclin I2.

Drug side effects: These drugs are potent pharmacologic agents and have known side effects. This is of especial importance because if they are to be used as preventive agents for coronary disease they must be given for prolonged periods of time; moreover, the side effects of years of drug use are largely unknown.

Aspirin: Among the patients considered for inclusion in the Coronary Drug Project Aspirin study, a significant number had to be excluded because of inability to tolerate aspirin or a history of peptic disease. Among those entered into the trial[51] there was a significantly increased incidence of abdominal pain, though not ulcer, among those taking aspirin. Blood urea nitrogen and uric acid levels were slightly elevated in the treated group, and the incidence of gout and podagra were significantly increased among those receiving aspirin.

Sulfinpyrazone: The sulfinpyrazone study[54] found no significant difference in the incidence of side effects in the treated versus the placebo group during the period of study; however, the mean follow-up period was only approximately 8.4 months. The manufacturer[76] notes problems with increased sensitivity to sulfonylurea hypoglycemic agents, sulfa drugs and coumarin anticoagulant agents. The drug is a potent uricosuric agent, and the possibility of precipitation of uric acid stones in the dehydrated patient must be considered. Peptic ulcers can be exacerbated with the drug, and severe blood dyscrasias, anemia, thrombocytopenia and agranulocytosis have been reported.

Dipyridamole: This agent is a vasodilator, and dizziness, headache, weakness and syncope occasionally result from its use.[77] Because it seems to dilate selectively the large coronary arteries, a coronary steal syndrome may be precipitated with a worsening of angina pectoris. Occasional gastrointestinal disturbances have also been noted.

Clofibrate: A wide variety of side effects have been reported with clofibrate.[76] Gastrointestinal problems, nausea, vomiting, dyspepsia, loose stools, flatulence and abdominal distress are the most common. Liver function tests may be affected. Results of the recent Cooperative Study[69] suggest an increased incidence of liver, gall bladder and intestinal diseases related to use of the drug. Patients often become more sensitive to coumarin anticoagulant agents. Fatigue, dizziness, headache and "flu-like" syndrome have been reported, as have cardiac arrhythmias, alopecia, renal dysfunction, leukopenia, anemia and impotence. Rarely, the cholesterol level may rise with the use of the drug. The litany of side effects with clofibrate is long, mainly because so many patients have been receiving the drug for long periods. In most patients clofibrate is well tolerated.

Beta adrenergic blocking agents: Side effects of the beta adrenergic blocking agents are well known and are primarily related to their antiadrenergic actions. These agents should be used with caution, if at all, in patients with diabetes, heart failure, asthma or chronic bronchitis or evidence of atrioventricular block.

Perspective on Antiplatelet Agents

In view of the theoretical benefit of antiplatelet aggregation therapy in the prevention of acute myocardial infarction and of progression of atherosclerosis, the suggestive data linking coronary risk factors with platelet abnormalities, the prospective studies that show a trend (although without statistical significance) toward benefit of aspirin in secondary prevention of infarction and the sulfinpyrazone study that has demonstrated a preventive effect in the short term, the disturbing data concerning a possible deleterious effect of these drugs because of inhibition of production of prostacyclin I2 and the possible side effects of long-term therapy with these drugs, the clinician is faced with the practical dilemma of whether and in what clinical circumstances these pharmacologic agents should be prescribed. First, although not discussed in this review, it should be noted that these drugs are indicated or at least worthy of trial for therapy of transient cerebral ischemic attacks and amaurosis fugax.[57,77] Second, it is considered appropriate to add these drugs to routine coumarin anticoagulation in a patient with a prosthetic valve who has had arterial emboli while on a well controlled anticoagulation regimen (not instead of coumarins but in addition to the coumarins).[73]

Recommended guidelines and indications for therapy: In patients with coronary artery disease the

indications for the use of these drugs are not yet proved beyond reasonable doubt, and the following recommendations are guidelines that I find useful while waiting for definitive data. I believe that the data tend to indicate that antiplatelet aggregating drugs have a beneficial effect. Although prostacyclin I2 inhibition theoretically may be detrimental, in no study have the patients treated with aspirin or sulfinpyrazone appeared to do less well than untreated control subjects, and in most trials there has been a trend toward benefit, even if the effect has not achieved statistical significance. While we await data from the AMIS study, the PARIS study, the Italian sulfinpyrazone study and further data from the Anturane study group, I consider it appropriate to use these drugs. The following dosages are currently being used when an antiplatelet aggregation effect is the aim of therapy: aspirin, 5 grains (325 mg) two or three times daily; sulfinpyrazone, 200 mg four times daily; dipyridamole, 50 mg four times daily; clofibrate, 500 mg three times daily; and propranolol, 20 mg four times daily.

The appropriate candidates for therapy are not known but, in order of priority, these are the patients for whom I consider therapy reasonable.

1. Patients with critical lesions on coronary arteriography who are not candidates for bypass surgery.
2. Patients who have had the intermediate coronary syndrome who do not undergo coronary arteriography.
3. Patients with a documented myocardial infarction who have recurrence of angina but who do not undergo coronary arteriography.
4. Patients with documented myocardial infarction, starting within 30 days of infarction.
5. Patients who have angina after coronary bypass surgery.
6. All patients with new angina.
7. All patients within 30 days of coronary bypass surgery (less definite indication).
8. All patients with chronic angina (less definite indication).

In these patients I try to make sure that one of the platelet-active drugs is being administered. If the patient is not receiving propranolol for angina or clofibrate for a lipid abnormality, I tend to favor aspirin or sulfinpyrazone as therapy because most of the supportive studies have used these drugs. It is important to make it clear to the patient that these regimens are a reasonable and possibly effective means of prophylaxis but that they are not yet fully proved to be of definite beneficial effect. If side effects develop, I will switch to another regimen; if that is not tolerated I discontinue the drugs.

Future implications: As time passes and more definitive data become available, the indications for these drugs can be expected to change. One hopes that these drugs will in time be proved effective and provide an important treatment for the patient with coronary artery disease. Meanwhile, although I believe that use of these drugs for their antiplatelet aggregation effect is already tentatively justified, the clinician must maintain an open mind and realize that the definitive efficacy of these drugs in the management of coronary artery disease has yet to be fully demonstrated.

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Anticoagulation in Myocardial Infarction: Modern Approach to an Old Problem

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The role of routine anticoagulation in acute myocardial infarction continues to be a source of controversy. There is currently strong evidence to suggest that conventional anticoagulation will prevent the formation of most deep vein thrombi and subsequent pulmonary embolization. Anticoagulant agents also appear to reduce the incidence of emboli from cardiac mural thrombi to peripheral arteries. Patients without a predisposition to bleeding are unlikely to have hemorrhagic complications in the hospital after usual doses of anticoagulant drugs. In patients with severe hypertension, prior gastrointestinal bleeding, carcinoma or advanced age, small dose heparin therapy appears to reduce the incidence of venous thrombosis and probably of pulmonary emboli as well. Its value in preventing peripheral arterial embolization has not been defined. Anticoagulation with standard "large" doses is an effective means of preventing the risks of pulmonary and peripheral emboli during the in-patient phase of acute myocardial infarction. Small dose heparin therapy provides an excellent alternative to conventional anticoagulation when there is more than a negligible risk of hemorrhage. There is little evidence at this time to support the use of long-term anticoagulation beyond the acute phase of myocardial infarction.

The introduction of heparin and the coumarin drugs into clinical medicine represented a major therapeutic advance. These are potent anticoagulant agents whose effects in vivo can be readily demonstrated and that offer promise for the prevention and management of many clinical problems in which thrombosis and embolism appear to play a role.

It was 30 years ago that Wright and his colleagues[1] in a major clinical trial for the American Heart Association recommended anticoagulation in patients with myocardial infarction. These investigators demonstrated that the anticoagulant drugs dicumarol and heparin reduced mortality in the first 6 weeks after acute myocardial infarction. The benefit was due largely to a reduction in potentially fatal thromboembolic complications. Although the study was not properly randomized, its conclusions led to the widespread use of anticoagulation in the United States. Yet, today, after multiple clinical trials of anticoagulation and its use in millions of patients, there is considerable confusion about its value in acute myocardial infarction. We present herein an interpretative review of the anticoagulation controversy and offer therapeutic recommendations in light of recent knowledge.

Objectives and Benefits of Anticoagulation

The potential advantages of anticoagulation in acute myocardial infarction include (1) prevention of thrombosis in the deep veins of the leg; (2) reduction in the incidence of embolization from cardiac mural thrombi to the brain, kidney or limbs; (3) prophylaxis against extension

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of myocardial necrosis or long-term recurrence of infarction; and (4) reduction of overall mortality related to myocardial infarction. In the following discussion we will analyze these potential benefits in relation to the risks of such therapy.

Effects of Anticoagulant Therapy on Deep Vein Thrombosis and Pulmonary Embolism

In 1961, Hilden et al.[2] reported on autopsies performed in 90 percent of 109 control patients (untreated with anticoagulant agents) who died of myocardial infarction. Sixteen percent of in-hospital deaths (representing 4 percent of the entire control population) were attributed to thromboemboli, the great majority of which involved the lungs. However, these studies were conducted at a time when 3 weeks of strict bed rest was prescribed for patients with infarction.

Later reports involving shorter periods of immobilization showed a somewhat smaller contribution of embolic deaths to the overall in-hospital mortality of patients with acute myocardial infarction. In the Veterans Administration Cooperative Trial,[3] 0.6 percent of 500 untreated patients had fatal pulmonary embolization. Wessler et al.[4] estimated that pulmonary embolization represents a danger to life in 5,000 persons or about 1 percent of the 500,000 annually admitted with myocardial infarction to hospitals in the United States. Because more than 90 percent of pulmonary emboli come from thrombi in the leg veins,[4] and because these are potentially preventable with anticoagulant therapy, it is important to analyze the frequency of deep vein thrombosis in patients with acute cardiac necrosis.

Incidence of deep vein thrombosis in acute myocardial infarction: The diagnosis of deep vein thrombosis in the leg on the basis of the physical examination is wrong in more than 50 percent of cases.[5,6] Moreover, autopsy studies may overestimate the true incidence of such thrombi. The use of the iodine-125 fibrinogen leg scanning technique has greatly improved diagnostic accuracy.[5–8] The radioactively tagged fibrinogen is incorporated into actively forming thrombi (many of these clinically silent), whose extent can be defined by external counters. Unfortunately, the method detects only thrombi located in the popliteal veins and calves, not those in the iliofemoral system.[8]

In seven reports[9–15] in which the iodine-125 fibrinogen scanning technique was used, the overall frequency of deep leg vein thrombosis after acute myocardial infarction ranged from 22 to 37 percent. Similar figures were reported for postoperative patients in a recent multicenter trial.[16] In patients with suspected myocardial infarction who are treated with bed rest but prove not to have cardiac damage, this complication appears to occur less frequently. For example, Murray et al.[9] performed fibrinogen scanning in 50 patients admitted with chest pain, and in 35 of these the diagnosis of myocardial infarction was eventually substantiated. In the group with infarction, the frequency of deep vein thrombosis was 34 percent. In patients similarly treated but later found to have no infarction, the incidence rate was 7 percent. These findings, confirmed in the studies of Nicolaides et al.,[10] suggest that a hypercoagulable state may exist after myocardial infarction, as it does after major surgery.[17]

Of importance is the finding of Maurer et al.[11] and others[10,15] that more than 50 percent of the thromboses destined to occur in the calf veins form within 72 hours of acute infarction, and 75 percent form within the first 5 to 7 days. These data indicate that any measure used to inhibit formation of thrombi must be used on admission to the hospital and should be effective almost immediately.

Predisposing factors: Although the overall incidence rate of deep vein thrombosis in the 1st week after an acute myocardial infarction is approximately 33 percent, the risk is particularly great in certain groups. For example, the presence of left ventricular failure increases the incidence rate to 40 to 50 percent, and the presence of shock to 50 to 60 percent.[11,14] The rate is also higher in patients with arrhythmias and preexisting angina pectoris.[14] Age is another important determinant: Emerson et al.[18] found incidence rates of deep vein thrombosis of 12.5 percent in patients less than 50 years old and of 71 percent in patients older than 70 years. Obesity, varicose veins and a history of myocardial infarction or thromboembolism also increase the danger.[17,18] These considerations suggest that it may be possible to define a high risk group in whom anticoagulation for prevention of deep vein thrombosis would be particularly effective.

Relation to pulmonary embolism: The relation of venous thrombosis in the legs to the life-threatening event of pulmonary embolism has been elucidated by Kakkar and collaborators.[19–21] From studies in postoperative patients that correlated fibrinogen scanning, ascending venography and clinical indicators of pulmonary emboli, these investigators concluded that (1) 75 to 80 percent of thrombi originating in the calf veins remain confined to that region and present essentially no danger of embolization; (2) 20 to 25 percent of these thrombi extend proximally to involve the popliteal and iliofemoral systems, this propagation usually occurring more than 3 days after initial formation of the thrombi in the calf; (3) 40 to 50 percent of the thrombi that spread proximally embolize; and (4) thrombi in the iliofemoral vessels almost never originate there but derive almost exclusively from proximal extension from the calf veins.

According to these principles, approximately 10 percent of deep vein thrombi that form in the calves will eventually lead to clinical pulmonary embolism and will prove fatal in up to one third of cases.[18,21,22] In the absence of evidence of thrombus formation in the leg scan, the incidence of pulmonary embolization would be expected to be small. This has been shown to be the case in patients sustaining a myocardial infarction or undergoing operative procedures (Table I). In this collected series of 452 patients who underwent scanning for thrombi, pulmonary emboli occurred in 10.3 percent of those with a positive scan and in no patient with a negative scan.

TABLE I

Reported Incidence of Pulmonary Emboli in Patients With and Without Deep Vein Thrombosis[21]

Study	Positive ^{125}I Scan (no. of patients)		Negative ^{125}I Scan (no. of patients)	
	Total	With Pulmonary Emboli	Total	With Pulmonary Emboli
Kakkar et al.[24]	40	4	92	0
Murray et al.[9]	13	4	37	0
Lambie et al.[25]	16	1	64	0
Hill et al.[23]	35	2	120	0
Hirsh[21]	12	1	53	0
Total no.	116	12	336	0
%	24	10.3	76	0

TABLE II

Reported Efficacy of Anticoagulation in Reducing Deep Leg Vein Thrombosis After Acute Myocardial Infarction

Study	Patients (no.)		Patients With Thrombosis (%)	
	Total	With Anticoagulation Therapy	Anticoagulation Group	Control Group
Nicolaides et al.[10]	31	18	5.5	38
Handley et al.[13]	48	24	0	29
Wray et al.[15]	92	46	6.5	22

Anticoagulant agents for preventing pulmonary emboli: If anticoagulation could substantially inhibit the formation of deep vein thrombi in the calves of patients with acute myocardial infarction it is possible that the frequency of pulmonary embolism might be diminished. The first premise—prevention of thrombosis with anticoagulant therapy—was confirmed in three studies (Table II) in which anticoagulant drugs reduced the incidence of thrombi, as assessed with leg scanning, by 80 percent. The efficacy of therapy in preventing pulmonary emboli has also been conclusively demonstrated (Table III). Anticoagulation therefore appears to be of value in forestalling deaths from pulmonary embolism in patients with myocardial infarction.

Effects of Anticoagulation on Peripheral Arterial Emboli

Emboli from the heart to the arteries of the kidneys, limbs or brain are usually easier to define clinically than are pulmonary emboli. Although the exact mechanism of thrombus initiation on the arterial side of the circulation (formation of a platelet plug) appears to differ from that on the venous side,[27] anticoagulant drugs may also be of value in this situation by preventing the propagation of a fibrin clot from the original platelet nidus. In fact, according to several studies[1–3,26] prophylaxis appears to be effective in reducing both morbidity and mortality from systemic embolization after acute myocardial infarction. The effect of anticoagulation in reducing the incidence of cerebral emboli complicating acute myocardial infarction is illustrated in Table IV.

In the American Heart Association study[1], the incidence of cerebral and peripheral emboli was reduced by two thirds. Hilden et al.[2] demonstrated a 24 percent incidence rate of cardiac mural thrombi at postmortem examination in patients receiving anticoagulant therapy as opposed to a 58 percent incidence rate in control subjects, although there was no significant difference in the incidence rate of peripheral emboli (3.6 versus 5.4 percent). In the British Medical Research Council report,[26] 24 patients (3.4 percent) in the group treated with phenindione had clinical occlusion of a systemic artery; only nine such incidents (1.3 percent) occurred among those who were treated with heparin as well. Similar percentages were found at autopsy. The Veterans Administration trial[3] found that 0.6 percent of 500 untreated patients admitted with myocardial infarction died of cerebral emboli; this mortality rate equaled that

TABLE III

Reported Efficacy of Anticoagulation in Preventing Pulmonary Embolization After Acute Myocardial Infarction

Study	Patients (no.)	Regimen	Deaths Due to Pulmonary Embolism* (%)	Clinical Incidence of Pulmonary Embolism* (%)	Pulmonary Embolism and/or Infarction at Autopsy† (%)
Wright et al.[1]	800	Anticoagulant drugs (432);	6	5.2	. . .
		No treatment (368)		9.4	
Hilden et al.[2]	800	Anticoagulant drugs (371);	1.4		5.0
		No treatment (429)	4.0		28.0
British Medical Research Council[26]	1427	Heparin and phenindione (712);	. . .	2.2	1.2
		Phenindione only (715)	. . .	5.5	5.6
VA Cooperative[3]	999	Anticoagulant drugs (500);	0.0	2.0	0.0/0.0
		No treatment (499)	0.6	4.8	32.0/9.7‡

* Percent of total patients with acute myocardial infarction.
† Percent of autopsies.
‡ 32.0 percent pulmonary embolism; 9.7 percent infarction.

TABLE IV

Reported Incidence of Cerebral Emboli in Acute Myocardial Infarction

Study	Patients (no.)	Incidence Rate: Control Group	Incidence Rate: Anti-Coagulation Group
Wright et al.[1]	800	4.9%	0.7%
British Medical Research Council[26]	1427	2.5%	1.1%
V.A. Cooperative[3]	999	3.8%	0.8%

from pulmonary emboli in the same series. Anticoagulation reduced the total number of clinical cerebral vascular accidents from 19 (3.8 percent) in the control subjects to 4 (0.8 percent) in the treated group. Embolization to the kidney and legs was completely prevented in the latter group, although eight such emboli (1.6 percent) were diagnosed clinically in untreated patients. Anticoagulation also halved the frequency of mural thrombi and peripheral emboli detected at autopsy. No treated patient died of cerebral infarction.

Extension of Myocardial Necrosis

In the British Medical Research Council study,[26] the in-hospital reinfarction rate for subjects given heparin and phenindione was not significantly different from that of the group receiving phenindione alone. These results were supported by the work of Drapkin and Merskey.[28] Similar findings were documented in the Veterans Administration Cooperative Trial,[3] in which both the short-term incidence of recurrent myocardial infarction and the frequency of deaths from reinfarction were essentially equal in the study populations.

Effect on In-Hospital Mortality

The best designed prospective studies available to date have demonstrated no improvement in the short-term death rates of patients with anticoagulation after myocardial infarction. Two recent retrospective trials[29,30] have rekindled the controversy, purporting to show a reduction in mortality in hospitalized patients; firm conclusions remain elusive. Wessler et al.[4] calculated that, because of the small overall incidence of deaths from embolism in myocardial infarction, a sample population of 38,000 would be required to demonstrate a statistically beneficial effect of anticoagulation on total mortality. It seems reasonable to suppose that such a study will not be undertaken. Nevertheless, a significant reduction in serious embolic events would presumably be reflected in prolonged survival.

Risks of Anticoagulant Therapy

Bleeding: Conventional anticoagulation therefore appears to be useful over the short term in reducing the incidence of deep vein thrombosis, pulmonary embolism and peripheral arterial embolism after myocardial infarction. This advantageous effect must be weighed against the risk of drug-induced hemorrhage, an eventuality that is particularly dangerous in the postinfarction patient. The magnitude of this risk is difficult to assess from published reports. Investigators have utilized widely differing anticoagulant regimens, have monitored anticoagulant effect with nonstandardized laboratory procedures and have sought various levels of interference with normal clotting processes. Only one major study[2] appears to have utilized anticoagulant agents in patients unselected for underlying hemorrhagic predispositions. Hilden et al.[2] reported four deaths due to bleeding (mortality rate 1 percent) in 371 patients treated with 50,000 units of heparin daily followed by dicumarol. The incidence rate of all hemorrhagic complications was 19 percent in the group treated with heparin versus 2 percent in the control subjects. No difference was noted in the incidence of cardiac rupture at postmortem examination, although nonfatal hemorrhagic pericardial effusion was three times more common in the anticoagulant-treated group.

Prevention of bleeding: Most studies have excluded from anticoagulant therapy patients over age 70 and those with known preexisting hemorrhagic diatheses, gastrointestinal ulceration, marked systemic hypertension, malignancy or hepatic disease. Such exclusion appears to reduce the incidence of serious hemorrhage. The British Medical Research Council[26] found clinical evidence of major hemorrhage in only 30 patients (4.3 percent) in the group receiving heparin and phenindione and in 8 others (1.1 percent) of those given phenindione alone. No deaths were attributed to bleeding. At autopsy, the two groups had equal rates of hemopericardium, subintimal hemorrhage and hemorrhagic infarction. Wray et al.,[15] Drapkin and Merskey[28] and Handley et al.,[13] using standard doses of 30,000 to 40,000 units of heparin daily, reported no increase in serious hemorrhagic complications. In the Veterans Administration Cooperative Trial,[3] major gastrointestinal bleeding occurred in 0.6 percent of both groups (heparin versus oral anticoagulant drugs), with no mortality caused by hemorrhage. Of importance is the finding by Emerson et al.[18] that the probability of fatal bleeding due to heparin therapy increased from 0.5 percent for those under age 70 years to 2.0 percent for those exceeding that age; the risks of anticoagulant therapy—as well as its benefits—may be magnified in the elderly.

Clinical implications: Proper patient selection may be of importance. Elderly persons with complicated infarction who are expected to be at bed rest for prolonged periods of time are at greatest risk of embolization. They are therefore most apt to benefit from anticoagulation. On the other hand, in those with a high likelihood of bleeding, as defined previously, anticoagulation might best be avoided. Emerson et al.[18] used sophisticated decision-making analysis to delineate those clinical situations in which the advantages of anticoagulation outweigh the potential for harm. They recommended heparin therapy only if the statistical risk of deep vein thrombosis exceeded 33 percent. This approach, of necessity, must be viewed as a compromise. Furthermore, no such stratification has been determined regarding peripheral arterial embolization.

Alternative Modes of Therapy

Physical methods to avoid deep vein thrombosis: Unfortunately, excluding a significant number of patients from anticoagulation because of fear of drug-induced complications may also deprive them of the potential advantages of such treatment. Several approaches have therefore been suggested in an attempt to maximize the effort to prevent thrombosis while minimizing the attendant risk of hemorrhage. One option is to avoid anticoagulation altogether and rely on physical measures to prevent deep vein thrombosis. Hill et al.[23] demonstrated the prophylactic value of intermittent pneumatic compression of the calf on the incidence of postoperative thrombus formation in patients without malignancy. Holford[31] showed that elastic stockings that provide graded compression from foot to thigh increase the rate of venous flow and thereby decrease the tendency to stasis and thrombosis. Physical methods, of course, would not be expected to affect the incidence of peripheral arterial emboli.

Early mobilization: Early ambulation after myocardial infarction appears to reduce significantly the incidence of deep vein thrombi. In a recent study, Miller et al.[32] performed iodine-125 fibrinogen scans daily for 5 to 7 days after myocardial infarction. They demonstrated that 10 percent of patients mobilized by the 3rd day had evidence of leg vein thrombi, whereas 60 percent of patients kept in bed for 5 days had a positive scan. Because thrombi formed within 72 hours of the infarction are almost invariably confined to the calf,[10,15,19] the hazard of pulmonary embolization at this stage is probably minimal. Unfortunately, the patients at greatest risk for thrombosis—those who are most ill—are the least likely to be candidates for early mobilization. Although potentially valuable, the early ambulation approach has yet to achieve widespread acceptance.

Antiplatelet drugs: These agents have recently been used to prevent venous thromboemboli.[33] If they prove efficacious, the ease of their administration and lack of associated bleeding complications would make them promising agents for future widespread use.

Role of Small Dose Heparin

Mode of action: A possible solution to the problem of anticoagulation in myocardial infarction has appeared with the recent advent of small dose heparin therapy. In 1962, Sharnoff et al.[34] introduced the use of small subcutaneous doses of heparin in the prevention of venous thrombosis in postoperative patients. Because the coagulation cascade acts as a biologic amplification system, minor perturbations early in the sequence may profoundly alter the reaction rates of subsequent steps. Small dose heparin therapy retards coagulation primarily by increasing the rate at which circulating antithrombin III (antifactor X_a) combines with, and inactivates, activated factor X.[35] With subcutaneous administration, plasma concentrations of the drug increase only slightly but are maintained at a constant level for many hours.[36] Because factor X acts at the beginning of the final stage of the coagulation process—before thrombin—a modest interference with its function is sufficient to effect a marked inhibition in clotting.[35] However, small doses of heparin are effective only if thrombin formation has not already occurred; these doses do not halt an ongoing thrombotic process.[37] The drug must therefore be given immediately after (or, in the case of elective surgery, before) the inciting event in order to be preventive.

Advantages: With the small dose regimen, the blood is never rendered totally incoagulable by the wide swings in plasma heparin concentration seen with conventional intravenous therapy.[36] As a result, the antithrombotic effect is achieved without significantly increasing the risk of bleeding. The clotting time is unaffected[38] and the partial thromboplastin time is only mildly prolonged,[39] thereby obviating specialized laboratory control. (A semisynthetic analog of heparin, very recently described,[40] may be even more specific in this regard.) Moreover, preliminary screening of the hemostatic mechanism is probably unnecessary in patients considered for prophylaxis.[41]

Efficacy in postoperative patients: The efficacy of heparin in small subcutaneous doses in preventing deep vein thrombosis after major surgery was demonstrated by Kakkar and collaborators in 1972.[42] This prospective randomized double blind study revealed a reduction in the incidence of calf thrombi from 52 to 8 percent (as determined by scanning with iodine-125–labeled fibrinogen) with 5,000 units of heparin given every 12 hours. Moreover, pulmonary embolism was recognized clinically in only one of 222 patients receiving prophylaxis. No increase in hemorrhagic manifestations was observed, even though patients were not preselected to exclude those with conditions that might increase the likelihood of bleeding.

In a larger randomized international study of 4,121 surgically treated patients,[16] a small dose heparin regimen (5,000 units subcutaneously every 8 hours) significantly reduced both thrombotic and pulmonary embolic postoperative complications. This benefit was achieved without increasing the risk of serious bleeding even in these patients with recent surgical wounds.

Efficacy in acute myocardial infarction: Warlow et al.[43] applied similar principles to a study of 127 patients with myocardial infarction. A regimen of small dose heparin was begun within 12 hours after the onset of infarction and continued at a level of 5,000 units every 12 hours for 10 days. Iodine-125–labeled fibrinogen scanning was performed. In this randomized double-blind trial evidence of calf vein thrombosis developed in 17.2 percent of control patients and in only 3.2 percent of those treated with small dose heparin. No hemorrhagic complications were noted.

In a combined medical and surgical series, Gallus et al.[39] reported on the administration of small dose heparin three times daily in 78 patients admitted with suspected myocardial infarction. The patients' legs were scanned with iodine-125–labeled fibrinogen for 10 days, and the frequency of venous thrombi was found to be 2.6 percent in treated patients and 22.5 percent in control subjects. The value of therapy appeared to be

particularly striking in patients with congestive heart failure. Moreover, phlebography revealed a reduction not only in the incidence of calf vein thrombi but also in the rate of propagation to the iliofemoral vessels. No pulmonary emboli occurred in this small group of patients.

Heparin in small doses thus appears to be effective in eliminating deep vein thrombi without increasing the danger of bleeding, even in patients at high risk of hemorrhage. Whether small dose heparin can also reduce the incidence of pulmonary emboli in myocardial infarction is not proved, although the experience in the postoperative studies and the work of Gallus et al.[39] suggest that it may be of great value. No data are yet available regarding the effect of heparin on mural thrombi or peripheral emboli.

Long-Term Prevention of Recurrent Myocardial Infarction

Rationale of long-term anticoagulation: The rationale for suggesting oral anticoagulation for several years after myocardial infarction as a means of preventing recurrence rests on the assumptions that thrombosis is an integral part of the atherosclerotic process[44,45] and that the sudden formation of a clot in a major coronary artery is the precipitating event in acute myocardial infarction.[45] Neither hypothesis has been conclusively validated. The nature of atherogenesis is still a hotly debated issue, and the role of thrombosis is unproved. Moreover, work by Roberts[45] strongly suggests that thrombi do not incite infarction but form when necrosis has already taken place. Erhardt et al.[46] injected iodine-125–labeled fibrinogen intravenously in seven patients soon after admission for acute myocardial infarction. At postmortem study, thrombi in the coronary arteries were found to have diffusely accumulated radioactivity, implying that clotting had followed, rather than preceded, the ischemic event. The validity of this conclusion has been challenged by Moschos et al.[47]

Results of therapy: Many clinical studies have investigated the effect of long-term anticoagulation on recurrent infarction and mortality.[48–52] Most studies have shown a slight decrease in the rate of recurrence of infarction, barely achieving statistical significance. There seems to be some value to anticoagulation in improving survival after myocardial infarction, but this benefit is restricted to men with a history of prolonged angina or previous episodes of cardiac necrosis.[52] Moreover, the advantage does not appear to persist beyond 2 to 3 years after initiation of therapy.[2,53] In addition, a large proportion of potential recipients of treatment (up to 50 percent in some series) were excluded from randomization because of advanced age or predisposition to bleeding. The methodologies of the long-term studies have been analyzed by Gross et al.[54]; in their review of published reports, no adequate experimental protocol was found.

Current Recommendations

Conventional heparin dosage followed by warfarin: We believe that all patients with definite or strongly suspected myocardial infarction should receive some form of anticoagulant therapy unless they are actively bleeding or suffering from a known hemorrhagic diathesis (congenital, hepatic or drug-induced). Because of the demonstrated value of large doses of heparin in preventing both peripheral and pulmonary embolization, patients who present no increased a priori risk of hemorrhage should ideally be started on a regimen of conventional (large) doses immediately on admission to the hospital. Anticoagulant drugs may be discontinued after 72 hours if the diagnosis of myocardial infarction is not substantiated. However, patients with bona fide myocardial infarction should be given heparin and then warfarin while at bed rest, then warfarin alone (monitored with prothrombin times) when walking begins. Anticoagulation should be maintained for 3 to 4 weeks after infarction to provide protection against the formation of mural thrombi on nonendothelialized endocardial surfaces. There appears to be no clear advantage to prolonging anticoagulation beyond this period of time.

Small dose heparin therapy: In patients over age 70 years and in those with malignancy, severe hypertension or preexisting gastrointestinal bleeding, the likelihood of hemorrhage with usual doses of anticoagulant drugs appears to be increased. Heparin should not be entirely withheld from these patients but administered in small doses, with the goal of preventing deep vein thrombosis and pulmonary embolism. According to available evidence, this aim can be accomplished with negligible risk. Therapy should be given during the period of bed rest and for several days thereafter. Despite the added risk of bleeding, the full dose treatment regimen is probably mandated, even in these patients, when active thrombosis is known to be occurring (small doses are ineffective), or when ventricular aneurysm, frequent arrhythmia or a previous arterial embolic event magnifies the danger of fatal cerebral embolization (for which the value of small doses of heparin is unproved).

Rational use of anticoagulant therapy in the setting of acute myocardial infarction may save more than 8,000 lives a year in this country. Full advantage should be taken of this therapeutic opportunity.

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New Developments in the Detection and Prevention of Venous Thromboembolism

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The recent development of relatively noninvasive, sensitive and specific procedures has been responsible for new information in the pathophysiology and epidemiology of venous thrombosis. Primary emphasis has been placed on detection of thrombosis with the radioactive fibrinogen leg scan, Doppler ultrasonic recording and, more recently, electrical impedance plethysmography. The latter procedure is easily performed by trained technicians; it is also sensitive and specific and provides an immediate answer. In 95 percent of patients with angiographically confirmed pulmonary embolism, results of impedance plethysmography were abnormal, indicating deep vein thrombosis and thus establishing the relation between the site of thrombus formation and pulmonary embolism. In 90 percent of patients suspected of having pulmonary embolism, when the plethysmogram indicated deep vein thrombosis, pulmonary angiograms revealed pulmonary embolism; similarly, when the plethysmogram was normal, pulmonary angiograms revealed normal findings in 90 percent of the patients. Hence, objective, noninvasive assessment of the deep venous system can be an excellent diagnostic aid, particularly when ventilation/perfusion scanning or pulmonary angiography is not readily available.

The most widely studied measure to prevent venous thrombosis has been treatment with subcutaneous small dose heparin. Although extremely effective in patients undergoing elective general surgery, this treatment has not been as effective or as appropriate in high risk patients, such as those undergoing hip, urologic or neurosurgical procedures, or in patients with malignancy. Among medically treated patients, it has been quite effective in those with acute myocardial infarction. Dextran has not been very effective in patients undergoing general surgery, although its use with relatively large volumes has resulted in favorable results in patients having hip surgery. Platelet antiaggregating agents have generally been disappointing prophylactic agents. The most recent and promising technique is intermittent pneumatic boot compression of the calves, which does not require medications that may alter blood coagulation. The results of this procedure have been impressive in general surgical, neurosurgical and urologic patients, conflicting in patients with hip surgery and poor in patients with malignancy undergoing surgery. In these groups of high risk patients, further investigations with new agents or methods or combined techniques are indicated.

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During the past decade, significant advances have been made in the understanding of the pathophysiology of venous thrombosis. In general surgical patients, particularly those undergoing elective abdominal or thoracic surgery, Kakkar et al.[1] noted that the early formation of thrombi appears to take place in the soleal veins of the calf, as identified with the radioactive fibrinogen leg scan. In approximately 78 percent of these patients with a positive scan, the test becomes negative, indicating dis-

appearance of the thrombus, or the test remains positive, but the thrombi are confined to the calf; in the remaining 22 percent, the thrombi will extend into the posterior tibial vein and subsequently into the popliteal vein. For clinical purposes, the popliteal veins may be considered the beginning of the deep venous system. Kakkar et al. also noted that because thrombi in the soleal veins detected with radioactive fibrinogen scanning were rarely associated with pulmonary embolism they were not considered dangerous, whereas those in the deep venous system were associated with pulmonary emboli and were considered dangerous. These observations are analogous to those made by Sevitt and Gallagher,[2] who noted in 1961 that virtually all patients who died of massive pulmonary embolism had deep vein thrombosis of the lower limbs when this was carefully searched for at autopsy.

These observations are relevant to the understanding of the relation between the site of thrombus formation and the occurrence of pulmonary embolism, when the thrombi are fragmented. They underlie current investigations into effective prophylaxis against deep vein thrombosis and pulmonary embolism. In addition, they have stimulated the development of objective, noninvasive methods to detect deep vein thrombosis in patients at risk for such thrombosis and also new methods to aid in the diagnosis of pulmonary embolism.

New Developments in Detection of Deep Vein Thrombosis

Although Doppler ultrasonic studies and the radioactive fibrinogen leg scan have been extensively investigated as tools for detecting deep vein thrombosis,[3,4] the more recently introduced procedure of electrical impedance plethysmography[5] appears to be gaining acceptance as the single best test for detecting deep vein thrombosis in the vast majority of patients. Hence, this review will be confined to this procedure and its newer applications. Our own investigations have been concerned with cuff impedance plethysmography as a diagnostic aid for detecting not only deep vein thrombosis, but also acute pulmonary embolism. Before the test could be used reliably in the clinical situation, several assumptions required further investigation: (1) The cuff impedance plethysmographic test is a sensitive and specific procedure to diagnose deep vein thrombosis; (2) many patients with deep vein thrombosis are asymptomatic; and (3) there is a strong relation between deep vein thrombosis and pulmonary embolism.

Impedance Plethysmography

Technique: In 1970, Wheeler et al.[5,6] published their data on a new application of electrical impedance plethysmography in detecting deep vein thrombosis. The noninvasive nature of the test was apparent (Fig. 1). The device consists of four electrodes fastened around the calf with Velcro® straps, a voltmeter and a strip chart recorder mounted in a compact portable case. The principle of the procedure is quite simple and derived from Ohm's law: $R = V/I$; the voltage required for a small, fixed amount of current to flow across the electrodes is proportional to the resistance encountered by the current. Because blood is an excellent conductor of electricity, the resistance is determined by the venous blood volume in the electrical field. In the original method, limb venous blood volume was regulated by respiratory maneuvers. During quiet tidal breathing, the intraabdominal pressure is low, posing little obstruction to the outflow of limb venous blood. However,

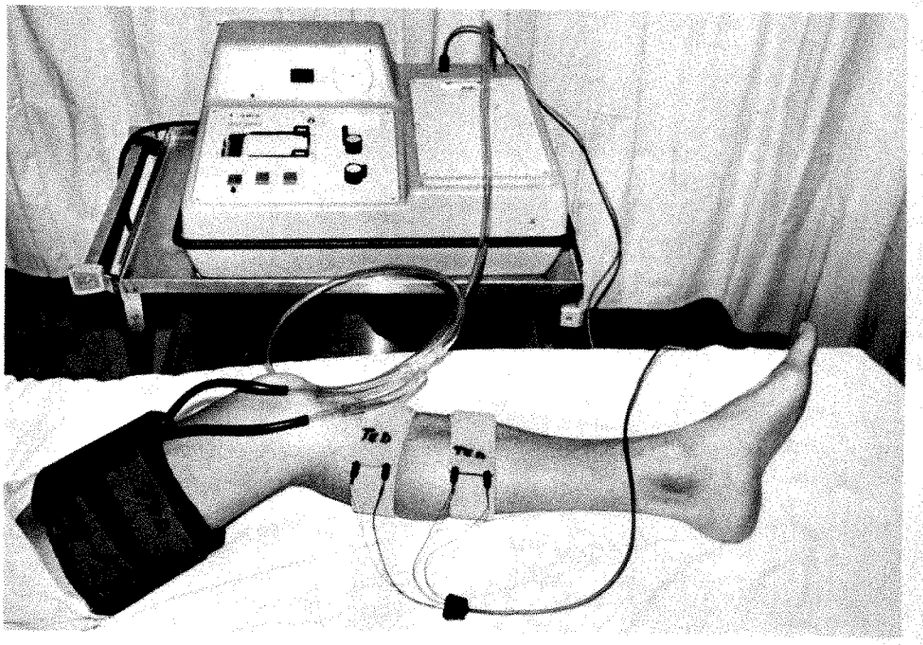


FIGURE 1. The basic equipment and method of electrode attachment for performing impedance plethysmography. The compact portable instrument contains a compressor to inflate the thigh cuff to a predetermined pressure and time duration, a voltmeter and a strip-chart recorder. The four electrodes are attached to convenient Velcro straps. The legs are sequentially studied.

during augmented inspiration and breath-holding, the intraabdominal pressure is increased, obstructing the outflow of limb venous blood, thereby augmenting limb venous blood volume. This results in a decrease in electrical resistance, and thus a decrease in voltage required for the fixed small amount of current to flow across the electrodes. When the held breath is released, thus reducing intraabdominal pressure, venous return from the limb is greatly augmented, decreasing limb venous blood volume. Hence, the resistance promptly increases, reflected in the increase in voltage necessary for the current to flow. In the normal state, then, the variations in the voltages recorded during the respiratory maneuvers reflect the changes in limb venous blood volume. In addition, the rapidity with which the voltage returns to the baseline value reflects the rapidity with which the limb venous blood volume returns to its baseline capacitance (Fig. 2).

In the abnormal state, such as that depicted by deep vein thrombosis, the voltage does not vary or varies less than the predicted normal, reflecting the subnormal changes in limb venous capacitance brought about by the respiratory maneuvers. This decrease in change in limb venous blood volume results from the intrinsic dilatation of the venous system caused by the occluding venous thrombus. Hence, augmented inspiration or breath-holding would add little additional volume to an already distended venous system, resulting in a relatively flat voltage recording. With release of the held breath, the predicted rapid return of the venous blood volume to baseline capacitance would not be observed because of the obstruction to venous return imposed by the deep vein occlusion. Thus, there is a flat voltage recording during augmented inspiration and breath-holding and a flat recording during the release phase. The slope of this voltage curve is directly related to the degree of deep venous obstruction by thrombi (Fig. 2).

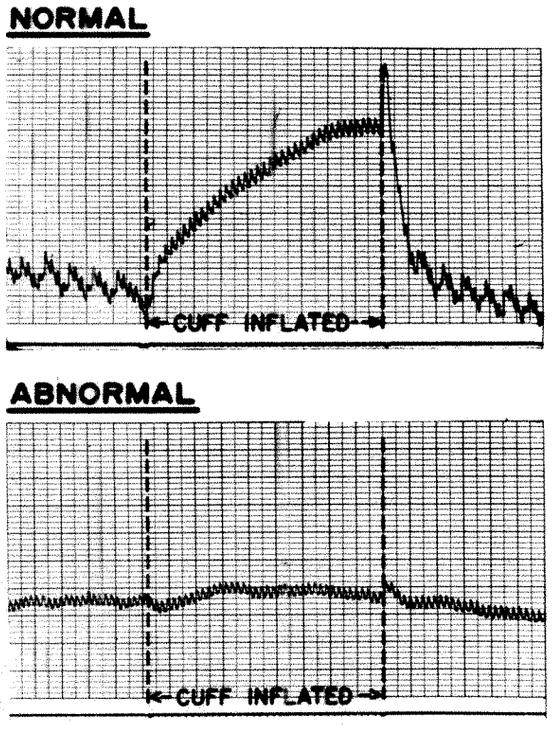


FIGURE 2. Characteristic pressure cuff impedance tracing from a normal subject **(top)** and an abnormal flat tracing from a patient with deep vein thrombosis **(bottom). Top panel,** rapid inflation of the thigh cuff to 40 cm of water for 45 seconds (previously achieved by augmented inspiration and breath-holding) results in a prompt decrease in voltage (superior direction) due to decreased resistance of an increased limb venous blood volume. Release of the cuff results in a prompt increase in voltage (inferior direction) due to increased resistance of a decreased limb venous blood volume. The variability of the voltage reflects the changing capacitance of a normal deep venous system. **Bottom panel,** there is little change on inflation or deflation of the cuff because of the constant dilation of the deep venous system caused by a thrombotic occlusion. The flatness of the curve indicates a virtually complete venous occlusion.

The major problem associated with the original technique was the inability to standardize the intraabdominal pressure generated by an augmented inspiration and holding of breath, thereby preventing accurate intra- and interpatient comparisons. Subsequent adoption of the thigh-cuff compression technique to 40 cm of water for 45 seconds eliminated the necessity for breath-holding and permitted standardization of the procedure.

Clinical Applications

Subsequent clinical investigations by several workers[7–10] showed impedance plethysmography to be a sensitive procedure for detecting deep vein thrombosis. In studies using venography as the standard, the sensitivity ranged from 93 to 100 percent (Table I). However, impedance plethysmography performed poorly in detecting superficial calf vein thrombi. Figures for detection of these thrombi range from 16 to 60 percent. However, this is not a serious clinical fault because there is little risk that calf vein thrombi will result in pulmonary emboli. As previously mentioned, the risk of embolization becomes high when such thrombi extend into the popliteal vein, the beginning of the deep venous system. In the patient at high risk for the development of venous thrombosis, daily or alternate day assessments with impedance plethysmography can be performed to detect deep vein thrombosis.

TABLE I

Accuracy of Impedance Plethysmography Versus Venography in Detecting Venous Thrombosis

Study	Number of Venograms	Detection With Impedance Plethysmogram DVT (%)	Calf VT (%)	NL (%)
Hallbook and Ling[7]	106	100	60	0
Cranley et al.[9]	302	96		2
Johnston et al.[8]	85	100	33	9
Wheeler et al.[5]	168	98	16	2
Hull et al.[10]	346	93	17	3
Mean		97	44	3

DVT = deep vein thrombosis; NL = normal; VT = vein thrombosis.

Asymptomatic patients with deep vein thrombosis: These clinical investigations concerning the pathophysiology and detection of venous thrombosis have led to the conclusion that a significant number of patients with established deep vein thrombosis are asymptomatic. They do not complain of leg pain; there is no obvious skin temperature elevation; there is no calf circumferential measurement difference (from the other limb) and Homan's sign is absent.[2,11,12] In our own series, approximately 60 percent of patients with positive impedance plethysmographic tests were asymptomatic. Hence, it becomes important to employ an objective procedure to assess the deep venous system. The traditional bedside examination can no longer be relied on for an accurate assessment of the patency of the deep venous system.

Relation of deep vein thrombosis and pulmonary embolism: Further investigations in our patients suspected of having pulmonary embolism revealed that 95 percent of those with pulmonary embolism confirmed with selective pulmonary angiography had an abnormal impedance plethysmographic study indicative of deep vein thrombosis (Table II). In addition, when pulmonary embolism was suspected, if the plethysmogram was abnormal and indicated deep vein thrombosis, pulmonary angiography revealed an intravascular filling defect or a vessel cutoff diagnostic of pulmonary embolism in 90 percent of the patients (Table III). On the other hand, if the impedance plethysmogram was normal in these patients with suspected embolism, the results of pulmonary angiography were negative in 90 percent.[12]

These data suggest that an objective assessment of the deep veins may be a very useful diagnostic aid in pulmonary embolism. Particularly in a busy emergency room, the application of cuff impedance plethysmography could differentiate patients with suspected pulmonary embolism who do not require lung scanning from those who should be hospitalized for further diagnostic studies. More selective utilization of nuclear medicine and angiographic facilities should result from such objective screening.

In-patient application of impedance plethysmography in a similar fashion is encouraged for patients suspected of having sustained pulmonary embolism in the hospital. However, until more precise data from a larger group of patients are available concerning the relation between plethysmographically detected deep vein thrombosis and pulmonary embolism, all patients with suspected pulmonary embolism should have, as a minimum, perfusion lung scanning. The addition of ventilation scanning adds to the specificity of the procedure. However, in patients with cardiopulmonary decompensation, the ventilation/perfusion scan may be misleading.

New Developments in Venous Thrombosis Prophylaxis

Recently, major efforts have been devoted to the study of small dose heparin, dextran, platelet antiaggregating agents and pneumatic boot compression as a means of reducing the incidence of venous thrombosis in various groups of patients at high risk. This communication is not intended to review the subject comprehensively, as admirably done by Gallus and Hirsh,[13] but rather to provide a selective overview of significant past studies and a careful look at the current and very promising method of pneumatic boot compression.

Small Dose Heparin

Results in surgically treated patients: The current investigations with small dose heparin prophylaxis for venous thrombosis are an outgrowth of the early studies of Sharnoff and DeBlasio[14,15] who used 5,000 to 10,000 units preoperatively and then 2,500 units at 6 hour intervals in the postoperative period. Although the incidence of pulmonary embolism was significantly reduced, the uncontrolled design of the study hindered acceptance of the efficacy of small doses of heparin in preventing venous thrombosis. Subsequently, Kakkar and associates,[16,17] using radioactive fibrinogen leg scanning, demonstrated the efficacy of small doses of subcutaneous heparin in preventing postoperative venous thrombosis (Table IV). In a subsequent large international multicenter trial organized by Kakkar,[18] small dose heparin prophylaxis was found effective in reducing the incidence of venous thrombosis from 25 percent in the control group to 8 percent in the treated group. In addition, the incidence of fatal pulmonary embolism, 0.77 percent in the control group, was reduced to 0.10 percent in the treated group. Gallus et

TABLE II

Deep Vein Thrombosis and Pulmonary Embolism: Relation Established With Pulmonary Angiography and Impedance Plethysmography

	Patients (no.)	Impedance Plethysmogram			
		Positive		Negative	
		no.	%	no.	%
Pulmonary angiogram					
Positive	36	34	95	2	5
Negative	22	4	18	18	82

TABLE III

Suspected Pulmonary Embolism: Probability of Pulmonary Embolism Based on Results of Impedance Plethysmographic Testing

	Patients (no.)	Pulmonary Angiogram			
		Positive		Negative	
		no.	%	no.	%
Impedance plethysmogram					
Positive (deep vein thrombosis)	38	34	90	4	10
Negative (no deep vein thrombosis)	20	2	10	18	90

al.[19], in a large study directed toward reducing popliteal and femoral vein thrombi, demonstrated a reduction in venous thrombosis from 16 percent in the control group to 4 percent in the treated group. In both of these trials, 5,000 units of heparin was given subcutaneously immediately before operation and then at 8 hour intervals in the postoperative period for 1 week or more, until the high risk period was over. Several smaller studies[20–28] assessing the effectiveness of the small dose heparin regimen have also been published (Table IV). In essence, they confirm the effectiveness of this form of prophylaxis in patients undergoing elective general energy.

The beneficial effects of small dose heparin were less apparent in patients undergoing hip and prostatic surgery and in those with malignancy who had surgery performed. The incidence of postoperative venous thrombosis in the control groups was considerably greater than in the control groups of patients undergoing elective general surgery. The incidence rate ranged from 37 to 54 percent in the untreated control patients undergoing hip surgery,[29,30] and ranged from 5 to 73 percent (mean 28 percent) in the treated groups.[29,31] Although the latter incidence rate is lower than in the control groups, it is considerably higher than that in a population of general surgical patients receiving small dose heparin therapy (6 percent).

In an innovative study of 84 patients undergoing total hip replacement, Sagar et al.[32] randomized patients into a small dose heparin group and a small dose heparin + dihydroergotamine group. Thirty-two concurrently studied patients received no treatment and served as a control group. The frequency of deep vein thrombosis, determined from the radioactive leg scan and venography, was 69 percent in the control patients, 32 percent in the group receiving small dose heparin and 16 percent in those receiving the combination of small dose heparin and dihydroergotamine. Both treatment groups showed significant differences from the control group. Nevertheless, the 16 percent incidence rate of deep vein thrombosis is considerably higher than the very low figure achieved in patients undergoing general surgery, and indicates that further studies are necessary in this high risk group to develop a really effective prophylactic procedure. This study also singles out dihydroergotamine, a potent venoconstrictor, as a promising adjunct to small dose heparin prophylaxis.

The incidence of venous thrombosis in patients undergoing urologic surgery ranges from 20 to 34 percent in control groups and 24 to 33 percent in treated groups receiving small dose heparin.[26,33] The data from these studies are difficult to interpret because of the wide variability of results, and they are not impressive, partly because all studies had a small number of patients. The current thought is that small dose heparin is less effective in urologic patients than in general surgical patients and that more effective means should be sought for this group.

Patients with malignancy undergoing surgery are at a particularly high risk of having venous thrombosis develop postoperatively. The incidence rate of venous thrombosis in control groups ranged from 22 to 59 percent, compared with 5 to 30 percent in the small dose heparin groups.[19,26,34] Again, although the incidence rate was lower in the treated group, it was generally higher than in patients without malignancy.

Results in acute myocardial infarctions: Although the vast majority of studies have assessed small dose heparin in surgical patients, the data from several studies of patients with acute myocardial infarction have been reported (Table V).[23,35–37] The earliest of these studies revealed no apparent benefit from heparin prophylaxis,[35] although subsequent studies demonstrated a degree of benefit similar to that observed in the general surgical patients. Nevertheless, internists and cardiologists are reluctant to use heparin prophylaxis routinely because of the presumed low incidence rate of clinical thromboembolism in myocardial infarction in this country. Many clinicians believe that the high reported incidence rate of venous thrombosis detected with radioactive fibrinogen leg scanning is an interesting laboratory finding that may not be clinically

TABLE IV

Small Dose Heparin Prophylaxis in General Surgical Patients Undergoing Elective Operation (venous thrombosis detected with fibrinogen leg scanning)

Series	Dose (qh)	VT in Control Group no.	VT in Control Group %	VT in Treated Group no.	VT in Treated Group %
Kakkar et al.[17]	q 12	17/39	42	3/39	8
Gordon-Smith et al.[20]	q 12	21/50	42	4/48	8
Nicolaides et al.[21]	q 12	29/122	24	1/122	1
Ballard et al.[22]	q 12	16/55	29	2/55	4
Gallus et al.[23]	q 8	19/118	16	2/108	2
Lahnborg et al.[24]	q 12	11/54	20	3/58	5
MacIntyre*[25]	q 12	47/128	37	15/128	12
Kakkar†[16]	q 8	164/667	25	48/625	8
Rosenberg et al.[26]	q 8	38/89	44	4/55	7
Strand[27]	q 12	10/50	20	3/50	6
Gallus et al.[19]	q 8	66/412	16	16/408	4
Gruber[28]	q 8	36/100	36	12/94	13
Total and mean		474/1884	25	113/1790	6

* Scottish Multi-center Trial.
† International Multicenter Trial.
VT = venous thrombosis.

TABLE V

Small Dose Heparin Prophylaxis in Patients With Acute Myocardial Infarction (venous thrombosis detected by fibrinogen leg scanning)

Series	Dose (qh)	VT in Control Group no.	VT in Control Group %	VT in Treated Group no.	VT in Treated Group %
Handley et al.[35]	q 12	7/24	29	6/26	23*
Warlow et al.[36]	q 12	11/64	17	2/63	3
Gallus et al.[23]	q 8	9/40	23	1/38	3
Emerson and Marks[37]	q 12	14/41	34	2/37	5
Total and mean		41/169	24	11/164	7

* Difference between control and treated groups not significant.
VT = venous thrombosis.

relevant. However, in a cooperative trial of anticoagulation in patients with acute myocardial infarction sponsored by the Veterans Administration,[38] the major difference was the reduced number of thromboembolic complications in the group treated with anticoagulant agents: 7.8 percent in the treated group versus 18.8 percent in the untreated control group. On the basis of these data, it is recommended that patients with acute myocardial infarction who are hospitalized receive prophylaxis for venous thrombosis. Until other investigations of other methods show superior results, small dose heparin is currently the prophylaxis of choice.

Dextran

Antithrombotic actions: Although the antithrombotic actions of dextran have been known for almost 20 years, the exact mechanism or mechanisms of these actions are not entirely known. Several suggested mechanisms include (1) stabilization of red cell suspensions[39]; (2) coating of endothelial surfaces with a protective layer, reducing the interaction with cell elements in the blood[40]; (3) reduction of platelet function at the sites of endothelial damage[41]; (4) alteration of red cell electrical charge[42]; (5) expansion of plasma volume resulting in hemodilution with subsequent decrease in blood viscosity and increase in local blood flow velocity[43–45]; and (6) alteration of thrombus structure (copolymerization of dextran with fibrin monomer) to make it more susceptible to endogenous lysis.[46,47]

Two preparations of dextran have been used in clinical trials: Dextran 70 (Macrodex®), with a molecular weight of 70,000, and dextran 40 (Rheomacrodex®), with a molecular weight of 40,000. Although it was initially thought that dextran 70 was biologically degraded to a molecular weight of 40,000, which is the active antithrombotic fraction, the two preparations are, in reality, handled differently in vivo.[48,49]

Results in surgically treated patients: Although a number of clinical trials to prevent venous thrombosis have been carried out with dextran, the results have been conflicting, primarily because the preparation, dosage and schedule protocols as well as the end point assessment procedures, have varied. In this brief survey of dextran efficacy, only those studies that used objective assessments, such as radioactive leg scanning or venography, or both, were selected for analysis (Table VI).

General surgery: In general surgical patients, several studies[50–52] showed favorable results, although the results of Gruber et al.[52] were not as favorable as the others nor as favorable as with small dose heparin in a comparable group. In contrast, other studies[53–56] showed no significant effects compared with findings in a control group. If one combines all these series into a single pool of patients (perhaps a statistically unsound procedure because of the differences in study protocol), venous thrombosis developed in 22 percent of the control patients and in 14 percent of those receiving dextran, which is hardly a striking difference.

Orthopedic surgery: Better results of dextran prophylaxis were reported in patients undergoing hip surgery. Of the six selected studies (Table VII), four showed favorable results,[57–60] and two[61,62] did not. The study by Evarts and Feil[59] was particularly revealing because a two dose regimen was used. When the standard dose of 500 ml/day was employed for approximately 10 days, the incidence rate of venous thrombosis was 26 percent, in contrast to 56 percent in the control group. However, when the dose was doubled to 1,000 ml/day for 10 days, the incidence rate was strikingly reduced to 6 percent, thus suggesting that this is the better prophylactic regimen.

Among the six selected series of patients undergoing orthopedic surgery venous thrombosis developed in 47 percent of the control group but in only 25 percent of the dextran treated group, a significant reduction. Although several of these studies had dramatic results, dextran is not an excellent prophylactic agent because of its potential for side effects, the need for daily intravenous

TABLE VI

Dextran Prophylaxis Against Venous Thrombosis in General Surgical Patients (detection with fibrinogen leg scanning or phlebography)

Series	Agent	VT in Control Group		VT in Treated Group	
		no.	%	no.	%
Jansen[50]	Dex 70	30/301	10	18/304	6
	Dex 40	. . .	. . .	13/296	4
Carter and Eban[51]	Dex 70	10/101	10	1/106	1
Becker and Schampi[53]	Dex 70	11/35	31	13/42	31*
Stephenson et al.[54]	Dex 70	4/35	11	10/34	29*
Ruckley[55]	Dex 70	47/128	37	32/128	25*
Kline et al.[56]	Dex 70	115/435	26	84/396	21*
Gruber et al.[52]	Dex 40	34/95	36	17/83	21
Total and mean		251/1130	22	188/1389	14

* Difference between control and treated groups not significant.
Dex = Dextran; VT = venous thrombosis.

TABLE VII

Dextran Prophylaxis Against Venous Thrombosis in Orthopedic Surgical Patients (detection with fibrinogen leg scanning or phlebography)

Series	Agent	VT in Control Group		VT in Treated Group	
		no.	%	no.	%
Johnsson et al.[57]	Dex 70	13/25	52	1/27	4
Ahlberg et al.[58]	Dex 70	16/45	36	5/39	13
Myhre and Holen[61]	Dex 70	22/55	40	11/55	20*
Evarts and Feil[59]	Dex 70	20/36	56	5/19	26
	Dex 70 (double dose)			2/31	6
Daniel et al.[62]	Dex 70	19/31	61	33/55	60*
Harris et al.[60]	Dex 40			15/61	25
	SDH			11/20	55*
	ASA, 1200 mg			18/51	36
Total and mean		90/192	47	72/287	25

* Difference between control and treated groups not significant.
ASA = Aspirin; Dex = Dextran; SDH = small dose heparin.

infusions and its considerable expense during the prophylactic period.

Platelet Antiaggregating Agents

Antithrombotic mechanisms: The clinical trials using agents that suppress platelet function as prophylaxis against venous thrombosis stem from several observations suggesting that platelets are involved in thrombosis formation. Platelet aggregates have been noted at the site of origin of venous thrombosis,[63,64] suggesting that they may initiate a thrombus by sticking first to a site of venous endothelial damage. The reported changes in platelet coagulant activity in patients undergoing hip surgery in whom venous thrombosis developed[65] and the shortening of platelet survival time and alterations in platelet adhesiveness in patients with recurrent venous thrombosis[66] appear to support this thesis. Because a number of agents can depress platelet function by impeding aggregability and adhesiveness, it seemed reasonable to investigate the in vivo effects of these agents in preventing venous thrombosis.

Reported clinical results in surgical patients: In an early study Browse and Hall[67] used dipyridamole in more than 600 general surgical patients. In the treatment group, 400 mg of the agent was administered daily. Unfortunately, the end point assessment of venous thrombosis was based on clinical recognition rather than on objective measures. The results showed no significant difference between the two groups: venous thrombosis developed in 4 percent and pulmonary embolism in 0.3 percent in the dipyridamole-treated group, whereas venous thrombosis developed in 2 percent and pulmonary embolism in 0.6 percent in the control group. The very low incidence rate of venous thrombosis in the control group, compared with findings in other similar studies in which radioactive leg scanning was used for diagnosis, strongly suggests that clinical assessment for venous thrombosis is not reliable and that no solid conclusions can be drawn from these data.

Five other reported studies were selected that were of reasonable design and that used either fibrinogen leg scanning or venography, or both, to confirm venous thrombosis in patients undergoing general surgery (Table VIII). Carter et al.,[68,69] in two studies that used several dose regimens of hydroxychloroquine, found a favorable result in general surgical patients. However, there were deficiencies in the protocol of their studies concerning maintenance of study blindness and objectivity and technique for diagnosing and confirming venous thrombosis. Nevertheless, on the basis of these favorable findings, we undertook to confirm these results in a similar group of patients, using impedance plethysmography to diagnose deep vein thrombosis confirmed with venography. However, we found no difference in 80 patients and terminated the study.

Similarly disappointing were the reported results[70,71] of aspirin prophylaxis in general surgical patients. The dosage appears not to be an important factor because the British Medical Research Council study[71] found no significant difference when 600 mg and a 2,400 mg regimen was used. In the most recent study of aspirin[72] in general surgical patients there was a favorable result: Venous thrombosis was noted in 20 percent of the control group but in only 6 percent of the treated group (Table VIII).

Clinical implications: Hence, there are three studies that suggest a beneficial effect from administering drugs that suppress platelet function, and two studies that do not. As a group, it might be calculated that venous thrombosis developed in 79 of 342 patients (23 percent) in the combined control group and in 78 of 380 patients (21 percent) in the combined treated group. It must therefore be concluded that the clinical trials of agents that suppress platelet function have been disappointing with respect to prophylaxis against venous thrombosis. The use of dipyridamole alone resulted in no difference between the treated and control groups although the study suffered from a lack of objective means of diagnosing venous thrombosis. Aspirin was not effective in the majority of studies. Hydroxychloroquine, with only one favorable report, probably would not yield similar data under a scientifically acceptable protocol. Therefore, platelet function-suppressing agents cannot be recommended for use in presenting venous thrombosis.

TABLE VIII

Prophylaxis With Platelet Antiaggregating Agents in General Surgical Patients (detection with fibrinogen leg scanning or phlebography)

Series	Agent & Dosage	VT in Control Group no.	%	VT in Treated Group no.	%
Carter et al.[68]	Hydroxychloroquine 600 mg/d	6/26	23	0/26	0
O'Brien et al.[70]	Aspirin 600 mg & 2400 mg/d	13/20	65	28/38	75*
BMRC[71]	Aspirin 600 mg/d	33/150	22	42/153	28*
Carter et al.[69]	Hydroxychloroquine 800 mg/d	17/97	18	5/107	5
Clagett et al.[72]	Aspirin 1300 mg/d	10/49	20	3/56	6
Total and mean		79/342	23	78/380	21

* Difference not significant.
BMRC = British Medical Research Council.

Physical Compression of Calf

Currently, many of the trials concerned with preventing venous thrombosis deal with methods of preventing stasis of limb venous blood. These attempts at prophylaxis are based on Virchow's postulate that venous stasis is an important factor in producing deep vein thrombosis. Particularly if changes in blood coagulation accompany stasis, as demonstrated dramatically in the rabbit by Wessler et al.,[73] or if there is associated venous endothelial damage, or both, venous thrombosis is destined to develop.

Because little can be done immediately to correct a "hypercoagulable" state or venous endothelial damage, attention has been directed toward the most manipulable of Virchow's triad—stasis of venous blood. Techniques subsequently devised to alter blood flow are of two types: (1) passive methods, and (2) active methods.

Leg elevation and elastic stockings: Passive methods presumably alter only velocity of venous blood flow, whereas active methods alter both velocity and volume of blood flow, a desirable feature in minimizing stasis within the venous valve cusps.[74] The earliest efforts to correct venous stasis concerned simple physical methods that passively increased the velocity of limb venous blood flow. These concerned the elevation of the dependent legs and the application of elastic wrappings or stockings. Although elevation of the legs to 15 to 20° will double the velocity of venous flow, there is no objective information that elevation before, during or after operation will reduce the incidence of deep vein thrombosis. Browse et al.,[74] in fact, found that the incidence of venous thrombosis was essentially the same as in the dependent control leg (16 versus 19 percent). The previous widespread practice of applying elastic hose was based on data from the uncontrolled clinical study of Wilkins and Stanton,[75] who concluded that the incidence of pulmonary embolism was reduced by elastic stockings.

Physical measures: Active measures to alter limb venous blood flow included early ambulation, mechanical and electrical measures to stimulate calf muscle activity and the technique of external pneumatic boot compression. Early ambulation has been widely considered on an empiric basis as a method of decreasing the incidence of venous thrombosis. However, there are no studies with objective assessments to support this view. On the other hand, a vigorous physical regimen consisting of leg elevation, use of elastic stockings and vigorous physiotherapy showed a slight reduction of venous thrombosis in patients undergoing general surgery.[76,77] Patients were not randomly selected in the study of Flanc et al.,[76] which compared the effect of peri- and postoperative use of these combined physical measures with that of routine physiotherapy alone. No overall effect of prophylaxis was noted, although there was a definite trend toward significance in treated patients over age 60 years. Tsapogas et al.,[77] in a very similar protocol, reported data that nearly reached significance for the treated group. However, because of the overall lack of convincing data, and because of the frequent attention and manpower required to implement such a vigorous regimen, this combination of physical measures cannot be recommended.

Calf muscle stimulation: Doran and White[78] demonstrated in 1967 that electrical stimulation of the calf muscles could increase velocity of limb venous blood flow. In addition, they concluded that the incidence of postoperative pulmonary embolism was reduced. Subsequently, other studies, using fibrinogen leg scanning to document venous thrombosis, were performed; three of these[79–81] revealed a significant effect from calf muscle stimulation, whereas two[26,82] demonstrated no significant effects. Overall, the technique appears to be quite effective in reducing deep vein thrombosis. However, its major disadvantages are that it is painful to the patient and must be employed under anesthesia at operation. Therefore, it is not suitable for daily use in the postoperative period.

Intermittent Calf Muscle Compression

Intermittent external pneumatic boot compression of the calf muscles has been studied as a noninvasive method of reducing the incidence of venous thrombosis. Although the complication of bleeding occurs rarely in patients receiving small dose heparin prophylaxis, this treatment is an invasive procedure that results in some prolongation of the clotting or partial thromboplastin time in 15 percent of patients.[83] Therefore, a great deal of attention has been diverted to the pneumatic boot, which should provide effective prophylaxis without altering the coagulant state of the blood.

General surgical patients: Several investigators, using fibrinogen leg scanning or venography in patients treated with pneumatic boot compression, have demonstrated very effective prophylaxis in general surgical patients (Table IX), as well as in higher risk patients such as those undergoing hip or neurosurgical procedures (Table X). In the early studies[84,85] the incidence of venous thrombosis was reduced from 31 to 33 percent to 5 to 10 percent. Subsequently, similar favorable findings were reported.[86–89] Lee et al.,[89] in an uncontrolled sequential comparison found that no deep vein thrombosis developed in 350 patients undergoing general surgery who had pneumatic boot compression during and after operation. In the year before the institution of such prophylaxis, venous thrombosis developed in 10 of 18 patients (55.5 percent) without

TABLE IX

Pneumatic Boot Compression Prophylaxis in General Surgical Patients

Series	VT in Control Group		VT in Treated Group	
	no.	%	no.	%
Sabri et al.[84]	12/39	31	2/39	5
Hills et al.[85]	23/70	33	7/70	10
Roberts and Cotton[86]	27/104	26	6/94	6
Taylor*	15/56	27	3/53	6
Clark[87]	7/36	19	0/36	0
Lee[88]	10/18	55		
Lee[89]			0/350	0
Total and mean	94/323	29	18/642	3

* Unpublished data: Taylor DF, Boonkoom V, Weyden HB: Pneumatic intermittent compression in prevention of deep thrombosis.

TABLE X

Pneumatic Boot Compression Prophylaxis in High Risk Surgical Patients

Series	Type of Surgery	VT in Control Group		VT in Treated Group	
		no.	%	no.	%
Cranley et al.[92]	Hip replacement	13/106	12	8/89	9*
Turpie et al.[90]	Neurosurgical	12/63	19	1/65	1.5
Skillman et al.[91]	Neurosurgical	12/48	25	4/47	8
Total and mean		37/217	17	13/201	6

* Difference between control and treated groups not significant.

prophylaxis. The study is weakened by the absence of concurrent control subjects but it is an impressive demonstration because of the absence of any venous thrombosis. Overall, in the general surgical patients from six investigational groups, venous thrombosis developed in 94 of 323 patients (20 percent) in the control groups but in only 18 of 642 patients (3 percent) treated with pneumatic boot compression.

Neurosurgery and hip replacement: In other groups of patients in whom small dose heparin prophylaxis would not be appropriate, as in neurosurgical patients, pneumatic boot compression has been very effective (Table X). In two studies[90,91] there was a significantly lesser incidence of venous thrombosis in the treated than in the control groups.

In contrast, patients undergoing hip replacements, a very high risk group not generally responding well to small dose heparin, did not respond beneficially to pneumatic boot compression in the early studies[92] (Table X). Subsequently, Lee et al.[89] reported excellent results in 193 patients undergoing surgery; deep vein thrombosis did not develop in any of the 24 patients who had hip procedures. Similarly, Bechtol et al.,[93] subsequent to a study of pneumatic boot compression prophylaxis in 157 patients with hip replacement, compared this group with two other groups treated with dextran and with warfarin. Deep vein thrombosis diagnosed clinically developed in 13 percent in the calf compression group but in 23 percent in the warfarin group and 20 percent in the dextran group. Although the authors considered pneumatic boot compression superior to the other two regimens, their study is weakened because of the sequential nature of the study groups and principally because no objective measures were employed to diagnose deep vein thrombosis. Harris et al.[94] in a novel study, investigated patients with previous venous thromboembolism undergoing hip replacement. Because of prior disease, baseline preoperative venograms were performed in each patient. On the basis of the venograms, patients were grouped into those with normal and those with abnormal preoperative venograms. The two groups were randomized into a pneumatic boot compression group or a warfarin group. In patients with normal preoperative venograms, there was no difference in incidence of venous thrombosis in those receiving pneumatic boot compression or warfarin prophylaxis. In patients with abnormal preoperative venograms, deep vein thrombosis developed in 10 of 18 patients (55.5 percent) receiving pneumatic boot compression for 4 to 5 days, compared with 5 of 20 patients (25 percent) receiving warfarin. Although these results did not quite reach significance, there was a strong trend in favor of warfarin.

Implications: With respect to the high risk group of patients with malignancy undergoing surgery, pneumatic boot compression was not beneficial. In one series,[85] venous thrombosis developed in 8 of 16 patients (50 percent) in the control group and in 5 of 9 patients (55 percent) in the treated group. Thus, further investigations are needed in the high risk group of orthopedic patients, those with malignancy undergoing surgery and perhaps urologic surgical patients. In general, these patients do not respond dramatically to any of the available means of prophylaxis. Perhaps a combination of measures would be more effective, as recently demonstrated by Sagar et al.,[32] who combined small dose heparin with dihydroergotamine. However, to be widely applicable, these combinations must still satisfy the criteria for optimal prophylaxis by being simple, noninvasive, safe and inexpensive.

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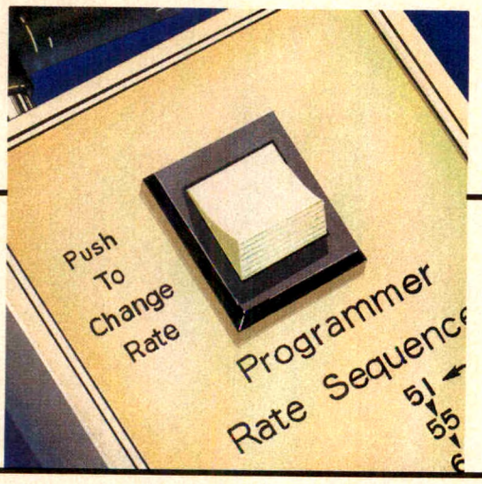
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1.

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3.



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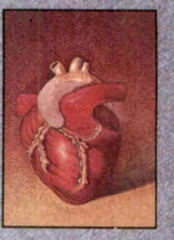
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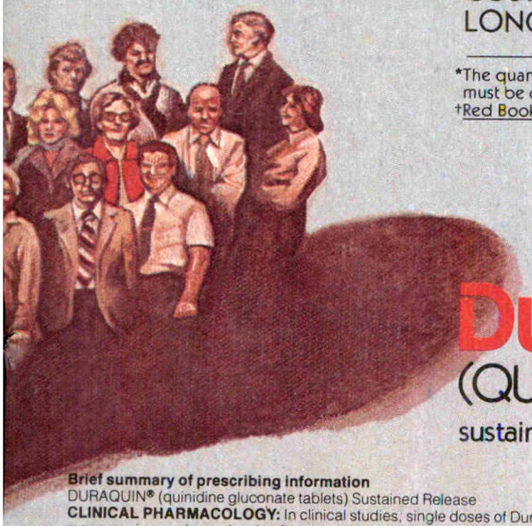
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Duraquin®
(QUINIDINE GLUCONATE TABLETS)
sustained-release tablets, 330 mg

Brief summary of prescribing information
DURAQUIN® (quinidine gluconate tablets) Sustained Release

CLINICAL PHARMACOLOGY: In clinical studies, single doses of Duraquin produced a mean maximum plasma level at 2 hours which was maintained for 12 hours. This broad plateau indicates slow, continuous absorption from the gastrointestinal tract.

In multiple dose studies, administration of Duraquin tablets, 660 mg every 12 hours, produced steady state (equilibrium) plasma levels shortly after 24 hours. The average quinidine plasma levels (Cramer and Isaksson assay [1]) were 0.81 mcg/ml and the mean peak levels were 1.16 mcg/ml in a group of normal male subjects weighing 75 Kg. Following the last dose at steady state, quinidine plasma levels decreased at an approximate rate of 50% in 10 hours. This compares to the expected plasma half-life of 6.3 hours for quinidine sulfate tablets, USP.

Therapeutic and toxic effects coordinate better with plasma levels than with dosage. While therapeutic levels of 3 to 6 mcg/ml with a range of 1.5 to 9 mcg/ml have been reported, these values are based on peak plasma levels determined by the less specific Edgar and Sokolow assay [2] This procedure yields quinidine levels averaging 22% higher than the Cramer and Isaksson assay. Plasma levels vary considerably in patients receiving identical doses. Therefore, it is advisable to adjust the dosage by monitoring plasma quinidine levels.

INDICATION: Duraquin tablets are indicated for the prevention of premature atrial, nodal, or ventricular contractions. They are also indicated for the maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion of atrial, nodal, or ventricular tachycardia, atrial flutter and fibrillation (either paroxysmal or chronic).

[1] Cramer, G. and Isaksson, B. Quantitative Determination of Quinidine in Plasma. Scandinavian J. Clin. & Lab. Investigation 15, 553, 1963.
[2] Edgar, A.L. and Sokolow, M. Experiences with the Photofluorometric Determination of Quinidine in Blood. J. Lab. Clin. Med. 36, 478, 1950.

CONTRAINDICATIONS: 1. History of hypersensitivity to quinidine manifested by thrombocytopenia, skin eruption, febrile reactions, etc.
2. Complete A-V block.
3. Complete bundle branch block or other severe intraventricular conduction defects exhibiting marked QRS widening or bizarre complexes.
4. Myasthenia gravis.
5. Arrhythmias associated with digitalis toxicity.

WARNINGS: 1. (a) In the treatment of atrial fibrillation with rapid ventricular response, ventricular rate should be controlled with digitalis glycosides *prior* to administration of quinidine.
(b) In the treatment of atrial flutter with quinidine, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine.

Recent reports have described increased, potentially toxic, digoxin plasma levels when quinidine is administered concurrently. When concurrent use is necessary, digoxin dosage should be reduced and plasma concentration should be monitored and patients observed closely for digitalis intoxication.

2. Quinidine cardiotoxicity may be manifested by increased PR and QT intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia. Appearance of these toxic signs during quinidine administration mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. Note: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia.
3. "Quinidine Syncope" may occur as a complication of long-term therapy. It is manifested by sudden loss of consciousness and ventricular arrhythmias with bizarre QRS complexes. This syndrome does not appear to be related to dose or plasma levels but occurs more often with prolonged QT intervals.

Brief summary continued on following page.

PD-JA-2299-1-P (3-79)

PARKE-DAVIS

PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, NJ 07950

Duraquin®
(QUINIDINE GLUCONATE TABLETS) sustained-release tablets, 330 mg

Brief summary continued from previous page.

4. Because quinidine antagonizes the effect of vagal excitation upon the atrium and the A-V node, the administration of parasympathomimetic drugs (choline esters) or the use of any other procedure to enhance vagal activity may fail to terminate paroxysmal supraventricular tachycardia in patients receiving quinidine.
5. Quinidine should be used with extreme caution in:
a) The presence of incomplete A-V block, since a complete block and asystole may result. Quinidine may cause unpredictable abnormalities of rhythm in digitalized hearts. Therefore, it should be used with caution in the presence of digitalis intoxication (see 1. (b) above).
b) Partial bundle branch block.
c) Severe congestive heart failure and hypotensive states due to the depressant effects of quinidine on myocardial contractility and arterial pressure.
d) Poor renal function, especially renal tubular acidosis, because of the potential accumulation of quinidine in plasma leading to toxic concentrations.

PRECAUTIONS:

1. Test Dose—A preliminary test dose of a single tablet of quinidine *sulfate* should be administered prior to the initiation of the sustained release gluconate to determine whether the patient has an idiosyncrasy to the Quinidine molecule.

2. Hypersensitivity—During the first weeks of therapy, hypersensitivity to quinidine, although rare, should be considered (eg, angioedema, purpura, acute asthmatic episode, vascular collapse).

3. Long-Term Therapy—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy and the drug should be discontinued if blood dyscrasias or signs of hepatic or renal disorders occur.

4. Large Doses—ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered.

5. Usage in Pregnancy—The use of quinidine, in pregnancy, should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus.

6. Nursing Mothers—The drug should be used with extreme caution in nursing mothers because the drug is excreted in breast milk.

7. General—In patients exhibiting asthma, muscle weakness, and infection with fever *prior* to quinidine administration, hypersensitivity reactions to the drug may be masked.

DRUG INTERACTIONS:

1. Caution should be used when quinidine and its analogs are administered concurrently with coumarin anticoagulants. This combination may reduce prothrombin levels and cause bleeding.
2. Quinidine, a weak base, may have its half-life prolonged in patients who are concurrently taking drugs that can alkalize the urine, such as thiazide diuretics, sodium bicarbonate, and carbonic anhydrase inhibitors. Quinidine and drugs which alkalize the urine should be used together cautiously.
3. Quinidine exhibits a distinct anticholinergic activity in the myocardial tissues. An additive vagolytic effect may be seen when quinidine and drugs having anticholinergic blocking activity are used together. Drugs having cholinergic activity may be antagonized by quinidine.
4. Quinidine and other antiarrhythmic agents may produce additive cardiac depressant effects when administered together.
5. Quinidine interaction with cardiac glycosides (digoxin). See WARNINGS.
6. Antacids may delay absorption of quinidine but appear unlikely to cause incomplete absorption.
7. Phenobarbital and phenytoin may reduce plasma $t_{1/2}$ of quinidine by 50%.
8. Quinidine may potentiate the neuromuscular blocking effect in ventilatory depression of patients receiving decamethonium, tubocurare, or succinylcholine.

ADVERSE REACTIONS: Symptoms of cinchonism (ringing in the ears, headache, disturbed vision) may appear in sensitive patients after a single dose of the drug.

Gastrointestinal: The most common side effects encountered with quinidine are referable to this system. Diarrhea frequently occurs, but it rarely necessitates withdrawal of the drug. Nausea, vomiting, and abdominal pain also occur. Some of these effects may be minimized by administering the drug with meals.

Cardiovascular: widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardias and fibrillation; paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.

CNS: headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata); optic neuritis.

Dermatologic: cutaneous flushing with intense pruritus.

Hypersensitivity reactions: angioedema, acute asthmatic episode, vascular collapse, respiratory arrest.

DOSAGE AND ADMINISTRATION: Dosage should be titrated to give the desired clinical effect, e.g., elimination of paroxysmal rhythm or reduction in premature contractions (See CLINICAL PHARMACOLOGY). This will often require prolonged ambulatory ECG monitoring, as hour-to-hour variability renders brief ECG recordings unreliable. When doses larger than 2.5 g/day are used, quinidine blood levels should be monitored, if possible, and serial ECGs should be followed (See WARNINGS and PRECAUTIONS).

For prevention of premature contractions and maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion, the usual dosage is from 330 mg to 660 mg every eight hours, most patients requiring the higher dose.

In elderly patients, and in patients in the lower end of the normal weight range, plasma quinidine determinations should be considered. Dosage adjustments may be required.

OVERDOSAGE: Cardiotoxic effects of quinidine may be reversed in part by molar sodium lactate; the hypotension may be reversed by vasoconstrictors and by catecholamines (since the vasodilation is partly due to alpha-adrenergic blockade).

HOW SUPPLIED: N 0071-0850 (P-D 850) Duraquin (quinidine gluconate tablets) 330-mg tablets are supplied in bottles of 100 tablets.

AHFS Category 24:04

YD

PARKE-DAVIS

Division of Warner-Lambert Company
Morris Plains, NJ 07950

SEARLE

Aldactazide®

(spironolactone 25 mg./ hydrochlorothiazide 25 mg.)

WARNING

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see ***Warnings***). Aldactazide should be used only in those conditions described in the ***Indications*** section of the complete prescribing information. Unnecessary use of this drug should be avoided.

Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edma is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytemegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist.

Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia.

Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions:

Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established.

Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness.

Adverse reactions are usually reversible upon discontinuation of Aldactazide.

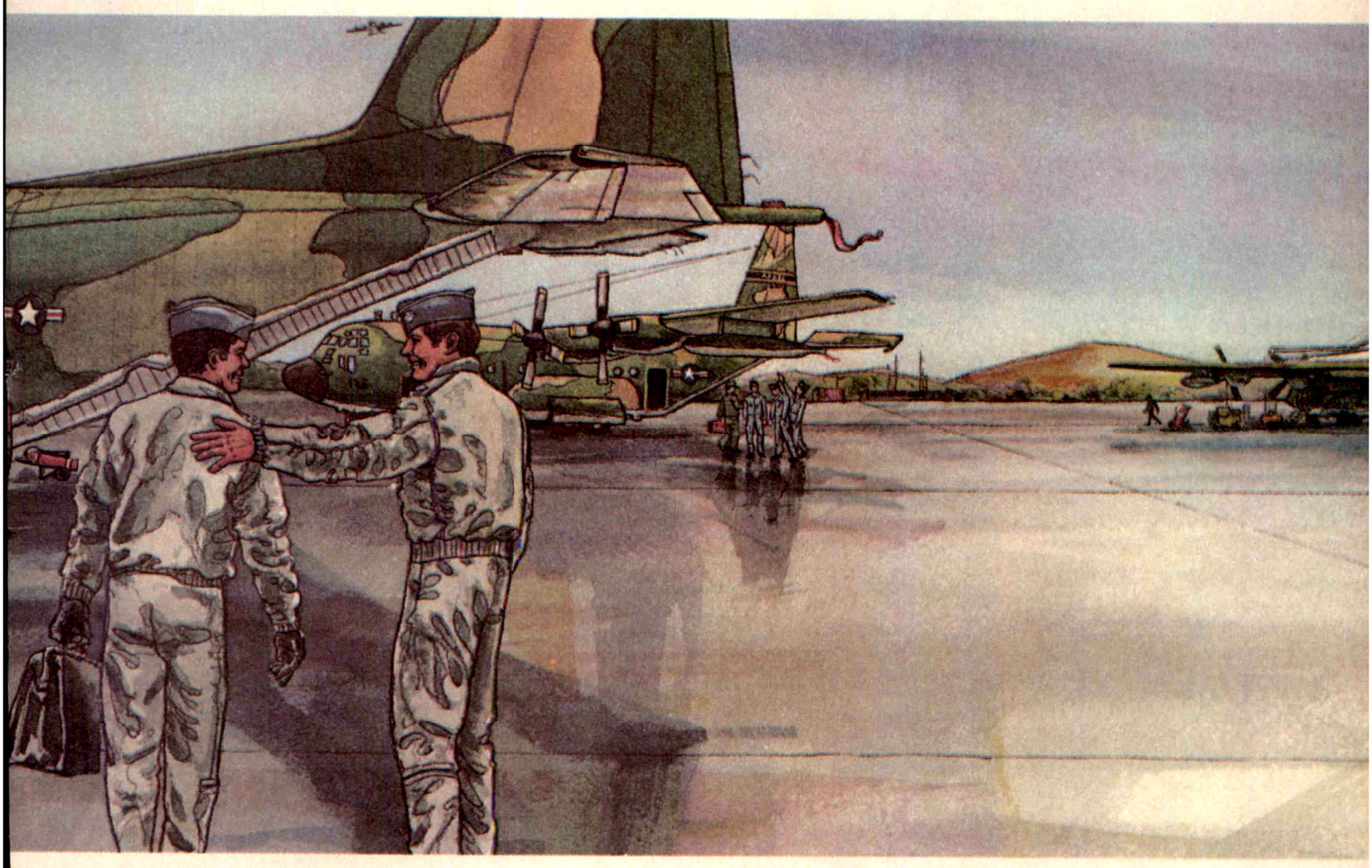
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1. Hull, D. H., and others: Treatment of Hypertension in Aviators: A Clinical Trial With Aldactazide, Aviat. Space Environ. Med. *49*:503-511 (March) 1978.

* While nondiuretic antihypertensive medications should be considered for the general hypertensive population unresponsive to thiazides, USAF determined that the demands placed on crewmembers of high-performance aircraft made these therapies inappropriate.

† The authors suggest that the high success rate in this particular study may have been due to the relative mildness of their patients' hypertension and to their concurrent adoption of corrective physiological measures.

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See next page for brief summary of prescribing information.

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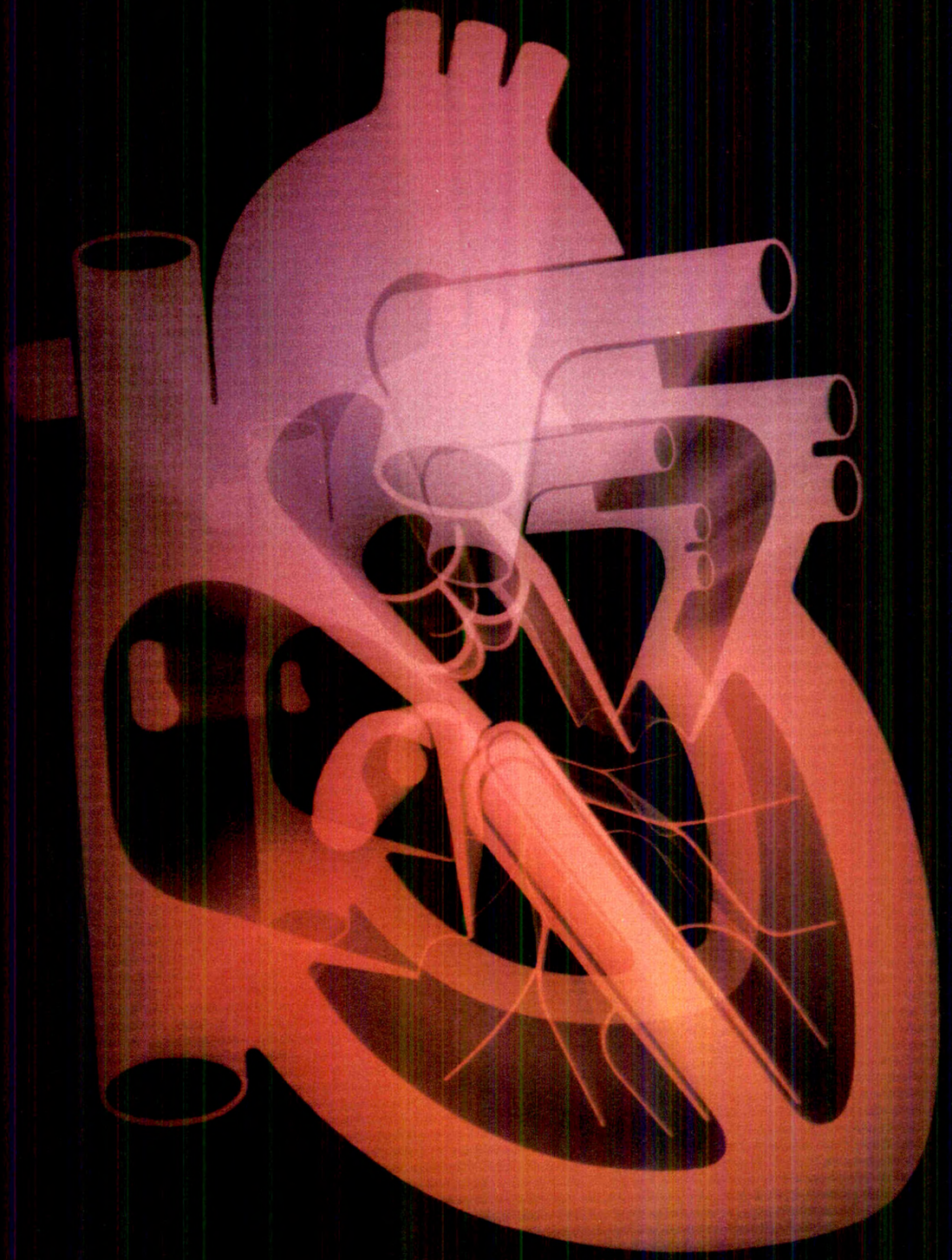
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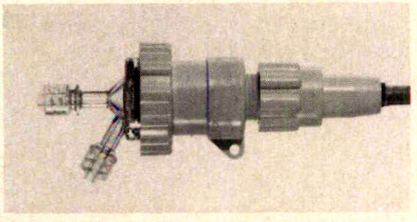
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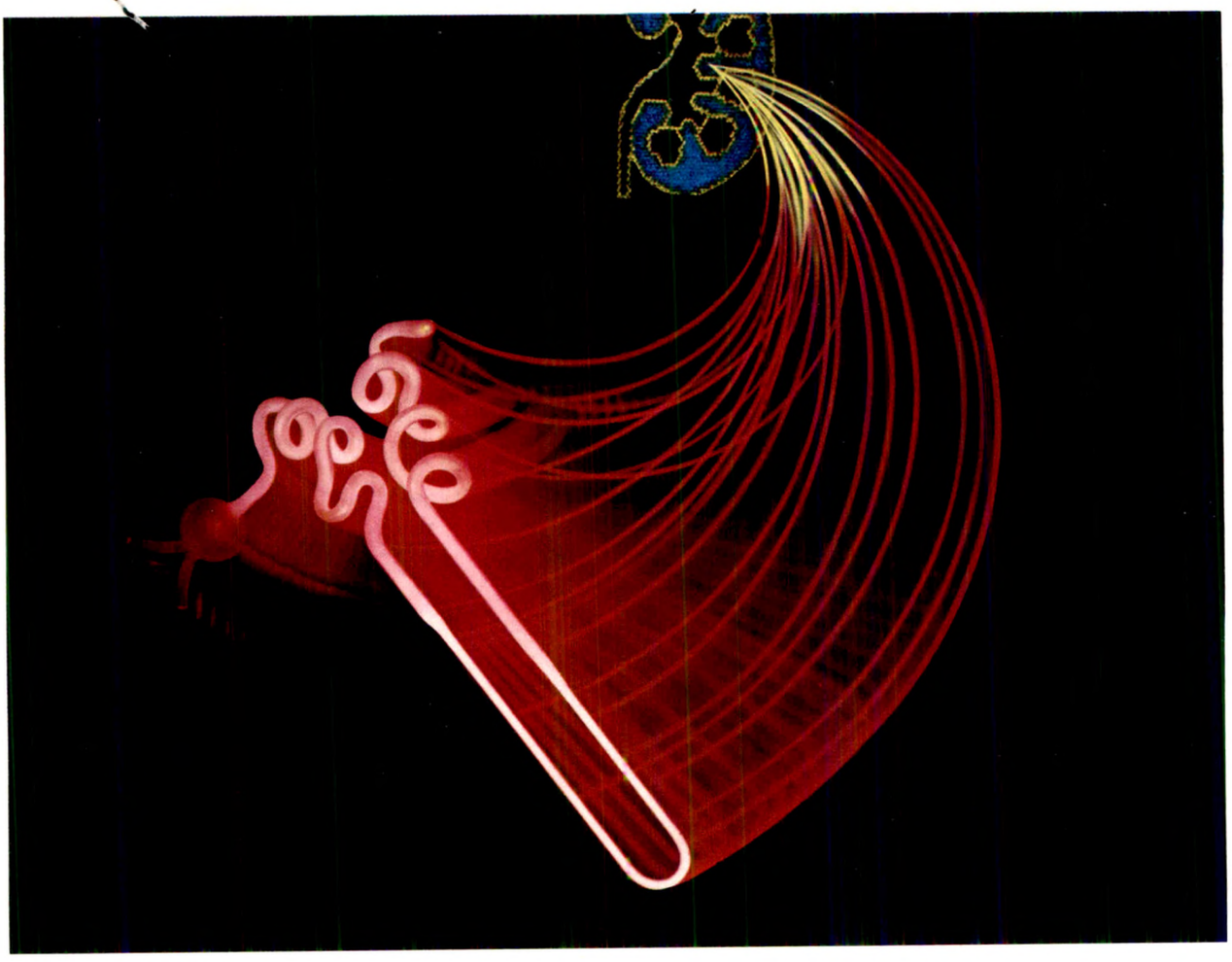
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Noninvasive Visualization of Coronary Arterial Aneurysm in Infants and Young Children With Mucocutaneous Lymph Node Syndrome With Two Dimensional Echocardiography

SATOSHI HIRAISHI, MD
KIMIO YASHIRO, MD, FACC
SHOICHI KUSANO, MD

Kanagawa, Japan

Real time two dimensional echocardiographic studies of the main coronary arteries were performed in 30 normal subjects and 58 patients with the mucocutaneous lymph node syndrome. Four echocardiographic coronary arterial patterns were observed: linear, dilated, fusiform or spherical. In normal subjects the left main coronary artery generally had a linear pattern but had a dilated pattern in two patients. The right coronary artery could not be visualized clearly. In 7 of the 58 patients with the mucocutaneous lymph node syndrome, a portion of the left main coronary artery had a fusiform or spherical pattern, or both, and the stem of the right coronary artery also had a spherical pattern in 2 patients. In all five patients who had coronary angiography, the procedure confirmed an aneurysm in the left main coronary artery or its branching point and the stem of the left anterior descending coronary artery or the stem of the right coronary artery, or both. In three of the five patients, coronary arterial aneurysms were predicted before coronary angiography was performed. Thus, two dimensional echocardiography is a reliable noninvasive method for evaluating coronary arterial aneurysms in infants and young children.

In 1967, Kawasaki[1] first described the mucocutaneous lymph node syndrome in infants and young children as a new clinical entity. It is an acute febrile illness with mucocutaneous involvement and is associated with swelling of the cervical lymph nodes. A survey, begun in 1970 by the Ministry of Health and Welfare of Japan, revealed that approximately 12,000 cases had been reported in that country by 1977.[2] This syndrome has also recently been reported in the United States, Canada, Greece, Australia and Korea.[3–10] The prognosis is usually good, but death occurs in 0.7 percent of patients, mainly as a result of cardiac lesions.[2,11] Aneurysms and thrombosis of the main coronary arteries have been noted in nearly all autopsy cases,[11,12] and coronary arterial lesions have frequently been demonstrated with coronary angiography in surviving patients with a history of this syndrome.[13–15]

Because the mortality and morbidity rates of coronary angiography are not always low, especially in patients with coronary arterial lesions,[16] the procedure should not be performed in the active stage of the syndrome. Therefore, noninvasive methods of determining the presence or absence of coronary arterial aneurysms would be of clinical value. In 1976 Weyman et al.[17] demonstrated the ability of two dimensional echocardiography to visualize the left main coronary artery in adult patients. In this study we evaluated the clinical usefulness and the reliability of this technique in detecting coronary arterial aneurysms in infants and young children.

From the Department of Pediatrics and Radiology, Kitasato University, Kanagawa, Japan. Manuscript received October 10, 1978; revised manuscript received January 2, 1979, accepted January 10, 1979.

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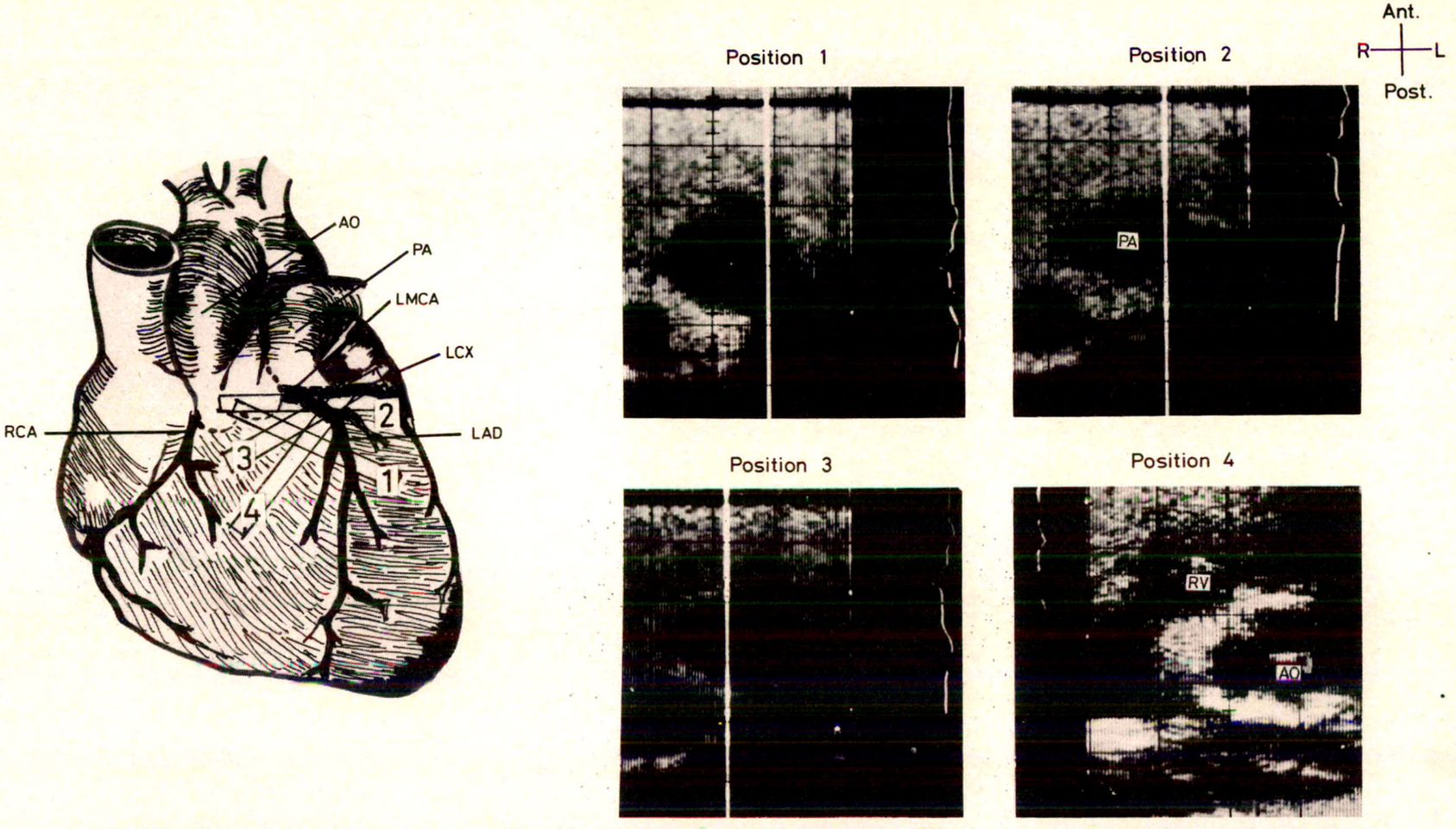


FIGURE 1. Left, diagram illustrating the relation of the position of the probe to the aorta (AO), pulmonary artery (PA) and main coronary arteries. **Right,** two dimensional echocardiograms of the normal left main coronary artery with different positions of the probe. The right coronary artery is not visualized clearly. A line shown on the echocardiogram is displayed to obtain the M mode tracing. The numbers are placed at the levels at which cross sections of the heart were taken. Ant. = anterior; L = left; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LMCA = left main coronary artery; Post. = posterior; R = right; RCA = right coronary artery; RV = right ventricle.

Methods

Patients: Two dimensional echocardiographic studies of the main coronary arteries were performed in 58 infants and children with the mucocutaneous lymph node syndrome. Serial echocardiographic recordings were also performed in 36 of these patients at 1 to 2 week intervals during the active stage of the disease. Of the 58 patients, 32 were male and 26 female; their ages ranged from 2 months to 10 years (mean 4 years). The diagnosis of this syndrome was made on the basis of criteria prepared by the Japanese Mucocutaneous Lymph Node Syndrome Research Committee in 1972.[18] Coronary angiography was performed in nine patients who were suspected to have coronary lesions on the basis of clinical and laboratory findings. A control group consisted of 30 normal children who had no heart disease as assessed from a history and physical examination; 12 were female and 18 male; their ages ranged from 3 months to 12 years (mean 5 years). They were evaluated for the adequacy of visualization of the coronary arterial structures and assessment of any causes of potential false positive diagnosis of coronary arterial aneurysm.

Echocardiographic studies: Two dimensional echocardiographic studies were performed using a commercially available electronic linear scanner (Aloka SSD 200, Aloka Company, Ltd., Tokyo, Japan.). A hand-held probe, 5 cm long and 1 cm wide, was utilized in each case. This probe contains a 3.5 megahertz, 60 element transducer adjusted to focus at 4 and 7 cm. The system is routinely operated at a rate of approximately 30 to 60 frames/sec which yields a line density of 100 lines/frame; the system results in a picture 4.5 cm in width and is adjustable to visualize the area within a depth of 15 cm. An electrocardiogram is displayed simultaneously on the oscilloscope to determine the timing. The clearest image obtained by electrocardiographic gating was selected, and its image was recorded on the Polaroid® photographs directly from the oscilloscope during the expiration phase when possible. Patients were examined in the supine or slightly left lateral position.

The position of the probe and its relation to the main coronary artery are shown in Figure 1. The probe is placed oblique to the left sternal border, along the long axis of the left ventricle, and the appearance of the aortic valve is the first orientation point. The probe is then rotated 30° to 40° counterclockwise, angled slightly above the chest wall, with the aorta to the right of the image. With this rotation, a dense "mass of echoes"* appears on the left border of the aorta and beneath the pulmonary artery or right ventricular outflow tract. The linear echo-free structure can be seen in this mass. This is the reference point for visualizing the left coronary artery (Fig. 1, position 1). With further counterclockwise rotation, the probe becomes parallel to the ribs in the area of the second or third left intercostal space posteriorly (Fig. 1, position 2). The probe is then set at position 3 with a further 10° to 15° rotation and with the beam directed slightly superiorly. During these procedures, the records are made at the point where the widest mass of echoes and the longest linear pattern in the mass are obtained.

The child is then placed in the left decubitus position and the probe is set in the area of the third and fourth intercostal space, with the beam directed to the right and superiorly to visualize the short axis of the aorta (Fig. 1, position 4).

* The term "mass of echoes," first used by Weyman et al.,[17] corresponds to dense echoes normally seen behind the pulmonary artery in the routine M mode echocardiographic examination of the pulmonary artery, described as the atriopulmonary sulcus by Gramiak et al.[19]

Results

Normal subjects: The left main coronary artery appears as a linear echo-free structure originating in the left inferior border of the aorta. In most patients, when the probe was placed in position 2 and the beam was directed perpendicular to or slightly above the chest wall, optimal planes were obtained. In these optimal planes, the left main coronary artery is bordered anteriorly by the pulmonary artery or the right ventricular outflow tract, posteriorly by a portion of the left atrium, to the right by the aorta and to the left by a portion of the left ventricle or the lung (Fig. 1).

Of 30 control subjects, 25 (83 percent) had satisfactory images of the left main coronary artery (more than 4 mm in length), but in 5 the images were less than 3 mm long. Twenty-seven (90 percent) also had a wide "mass of echoes" longer than 8 mm. In 23 of the 25 patients who had satisfactory images, the echocardiogram showed a linear pattern and in the other two a dilatational pattern. In three studies the branching point of the left main coronary artery could be visualized. In contrast, the stem of the right coronary artery could not be visualized clearly in any of the probe positions or directions tried. No fusiform or spherical pattern was observed in any subject with a carefully executed recording and interpretation.

Patients with the mucocutaneous lymph node syndrome: Satisfactory visualization of the left main coronary artery and of the wide "mass of echoes" was obtained in 51 of the 58 patients (88 percent). Forty-one of these patients had a linear pattern, three a dilatational, one a fusiform, five a spherical and one both a spherical and a fusiform pattern. In two patients a spherical pattern was found in the stem of the right coronary artery. In all 51 patients the same patterns were obtained repeatedly. Nine patients underwent coronary angiography in addition to two dimensional echocardiography, including seven whose echocardiogram revealed a coronary arterial aneurysm. Table I compares the angiographic and echocardiographic findings in these seven patients.

Only the estimated size of the aneurysm could be assessed in patients with continuous multiple aneurysms. The estimated size of the aneurysm and its distance from the ostium of the aorta may differ depending on the section of the aneurysm and coronary artery studied. The results of echocardiography and angiography were similar in the nine patients with both studies. Four patients who had a linear or dilatational pattern in the echocardiogram had a normal coronary angiogram. All five patients with a fusiform or spherical echocardiographic pattern were confirmed to have coronary aneurysms, one in the left main coronary artery, one in the branching point of this artery and in the right coronary artery, one in the stem of the left anterior descending artery, one in the left main coronary artery, the left anterior descending artery and the stem of the left circumflex artery, and one in the branching point of the left main coronary artery, the left anterior descending artery and the right coronary artery.

TABLE I

Two Dimensional Echocardiographic and Angiographic Data in Seven Patients With Mucocutaneous Lymph Node Syndrome

Case no.	Sex	Age	Size of Aneurysm (mm)							Distance From Ostium of Aorta to Aneurysm (mm)	
			2D Echo		Angio						
					LCA						
			LCA	RCA	LMCA	B	LAD	LCX	RCA	2D Echo	Angio
1	F	1 yr 4 mo	5 × 2, 4 × 3		6 × 4		6 × 5	6 × 6		3	4
2	M	4 mo	14 × 7	8 × 8		10 × 8	11 × 6		12 × 10	2	?
3	M	10 mo	4 × 2		7 × 5					4	?
4	F	3 yr 9 mo	4 × 4				5 × 4			8	8
5	M	2 mo	7 × 5	6 × 6		10 × 8			14 × 9	6	10
6	F	1 yr	2 × 2	—		—	—	—	—	3	—
7	M	6 yr	4 × 4	—		—	—		—	2	—

B = bifurcation of left main coronary artery; LAD = left anterior descending coronary artery; LCA = left coronary artery; LCX = left circumflex coronary artery; LMCA = left main coronary artery; ? = distance undefined; — = angiography not performed.

Figure 2 shows the echocardiographic image in Patient 4, who had an aneurysm of the stem of the left anterior descending artery confirmed with angiography. The size of the aneurysm and the distance from the ostium of the aorta to the aneurysm were approximately similar to those observed with subsequently performed coronary angiography. In this patient, a wider image of "mass of echoes" beneath the right ventricular outflow tract was useful in obtaining a clear image of the aneurysm of the left anterior descending artery (Fig. 3).

Figure 4 shows the echocardiogram and coronary angiogram from Patient 5 with aneurysms of the branching point of the left main coronary artery and the stem of the right coronary artery. An angiogram from this patient again demonstrates the similarity in appearance of the aneurysm observed with these two techniques.

Prospective study: In 5 of the 36 patients who had serial echocardiograms obtained during the active stage of the disease, a spherical or fusiform pattern was observed 2 to 4 weeks after the onset of the disease. The serial echocardiograms from Patient 6 are shown in Figure 5. All these patterns persisted for 2 to 10 months (in four patients), but in one patient this pattern disappeared in 2 months. Of the five serially studied patients who underwent coronary angiography, all three

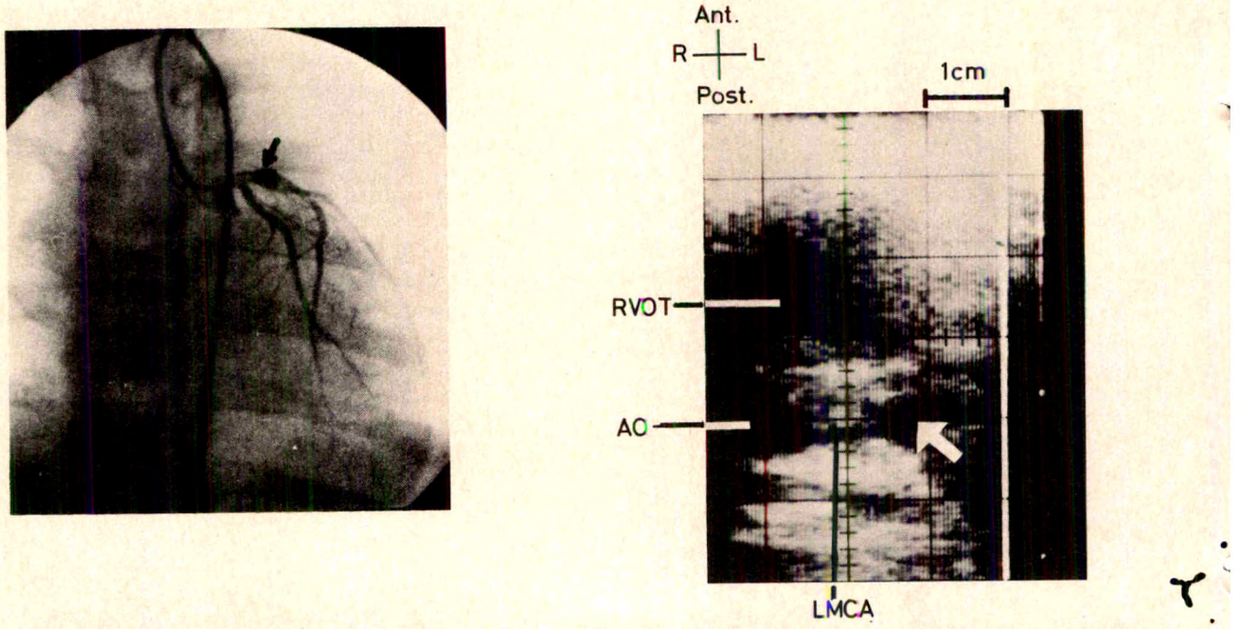


FIGURE 2. Case 4. **Left,** coronary angiogram in anteroposterior projection showing the aneurysm (**arrow**) of the left anterior descending coronary artery. **Right,** two dimensional echocardiogram. The left main coronary artery (LMCA) originates at the left inferior border of the aorta (AO) and extends laterally to communicate with a spherical echo-free space (**arrow**) representing the aneurysm. RVOT = right ventricular outflow tract; other abbreviations as in Figure 1.

with a positive echocardiogram were confirmed to have coronary arterial aneurysms. In one of the remaining two patients, followed up for 2.5 years (Fig. 6), a pattern suggesting formation of thrombus in part of the aneurysm was observed at the 2 years follow-up study, but it disappeared 6 months later, although the aneurysm persisted without changing in size.

Discussion

The mucocutaneous lymph node syndrome is a disease of unknown etiology and pathogenesis most frequently affecting infants and children less than 5 years of age.[20] One study[21] found, in the active stage of the disease, abnormal electrocardiographic patterns in almost all patients, cardiomegaly in 35 percent and abnormal heart sounds in 80 percent.[21] Pericardial effusion was detected with echocardiography in 8 of our 36 patients, and a marked decrease in left ventricular performance was observed in 3. These findings suggest that not only arteritis but also myocarditis and pericarditis occur in the active stage of the syndrome. Some investigators[13,14] found aneurysmal narrowing, tortuosity and obstruction of the coronary artery in 40 to 60 percent of surviving patients who underwent coronary angiography. Our study and a pathologic study[12] also demonstrated the presence of coronary aneurysms 2 to 4 weeks after onset of the syndrome. Thus, aneurysms may already be forming 1 to 2 weeks after the onset. The majority of reported deaths occurred in the 3rd or 4th week of the illness, but late death due to coronary artery disease and extensive myocardial infarction 1 to 8 years after the onset of illness has frequently been reported.[7,22–25]

Some authors[26,27] suggest that anticoagulant therapy including aspirin inhibits the formation of aneurysm and thrombus and may prevent sudden death. In children with severe coronary arterial obstruction and myocardial infarction, treatment with coronary bypass surgery is under investigation.[28,29] Therefore, early diagnosis of coronary arterial aneurysm and follow-up of these patients are extremely important. The detection of coronary arterial lesions with coronary angiography is accurate but is accompanied by some risk. Such information is not easily obtainable in the active stage because coronary angiography is generally performed after the active stage has completely subsided, as judged from clinical and laboratory findings.

Role of echocardiography in diagnosis of coronary arterial lesions: Noninvasive visualization of the main coronary arteries is therefore of clinical value. Weyman et al.[17] first demonstrated that it was possible to record the left main coronary artery utilizing a mechanical sector cross-sectional echocardiographic technique in adult patients. They confirmed that the structure visualized was in fact the left main coronary artery by injecting Cardiogreen® dye directly into the left main coronary artery. Matsuo et al.[30] also visualized a coronary arterial aneurysm in two children with the mucocutaneous lymph node syndrome by electronic sector two dimensional echocardiography.

We visualized the main coronary arteries utilizing the electronic linear two dimensional echocardiographic technique in infants and children. The advantages of the electronic multicrystal scanner are that a wider field and more accurate information, especially at short distances, can be obtained with less interference by the

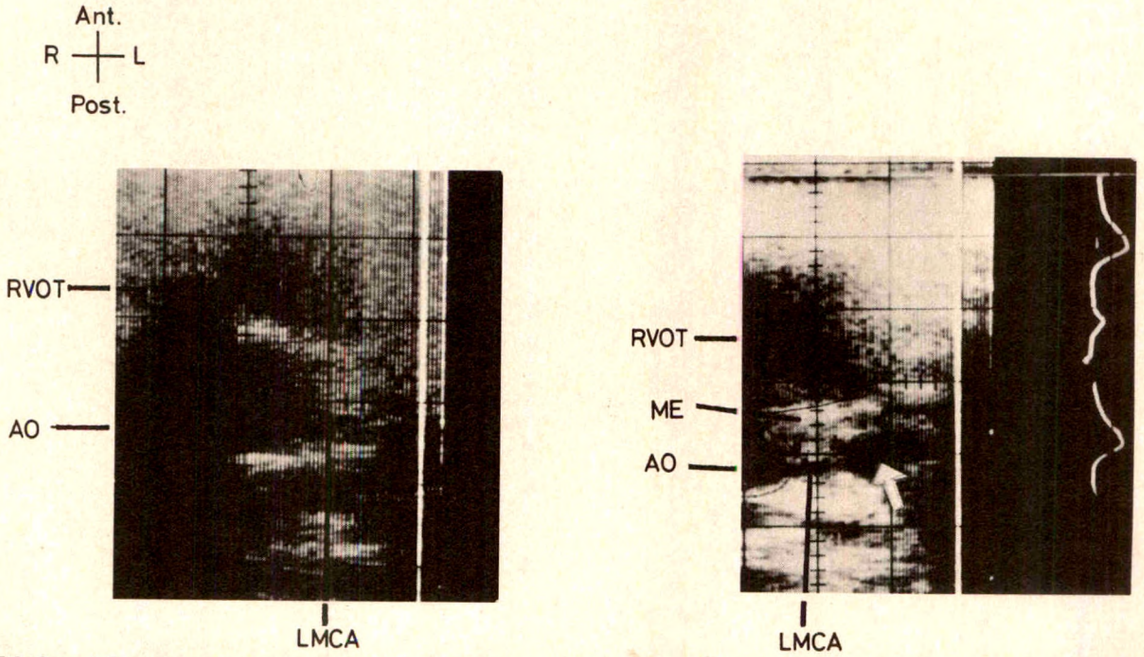


FIGURE 3. Case 4. Two dimensional echocardiogram from the same patient. The "mass of echoes" (ME) beneath the right ventricular outflow tract (RVOT) is wider in the right than in the the left echocardiogram. The aneurysm (**arrow**) of the left anterior descending coronary artery is clearer in echocardiogram at right. LMCA = left main coronary artery; other abbreviations as in Figure 1.

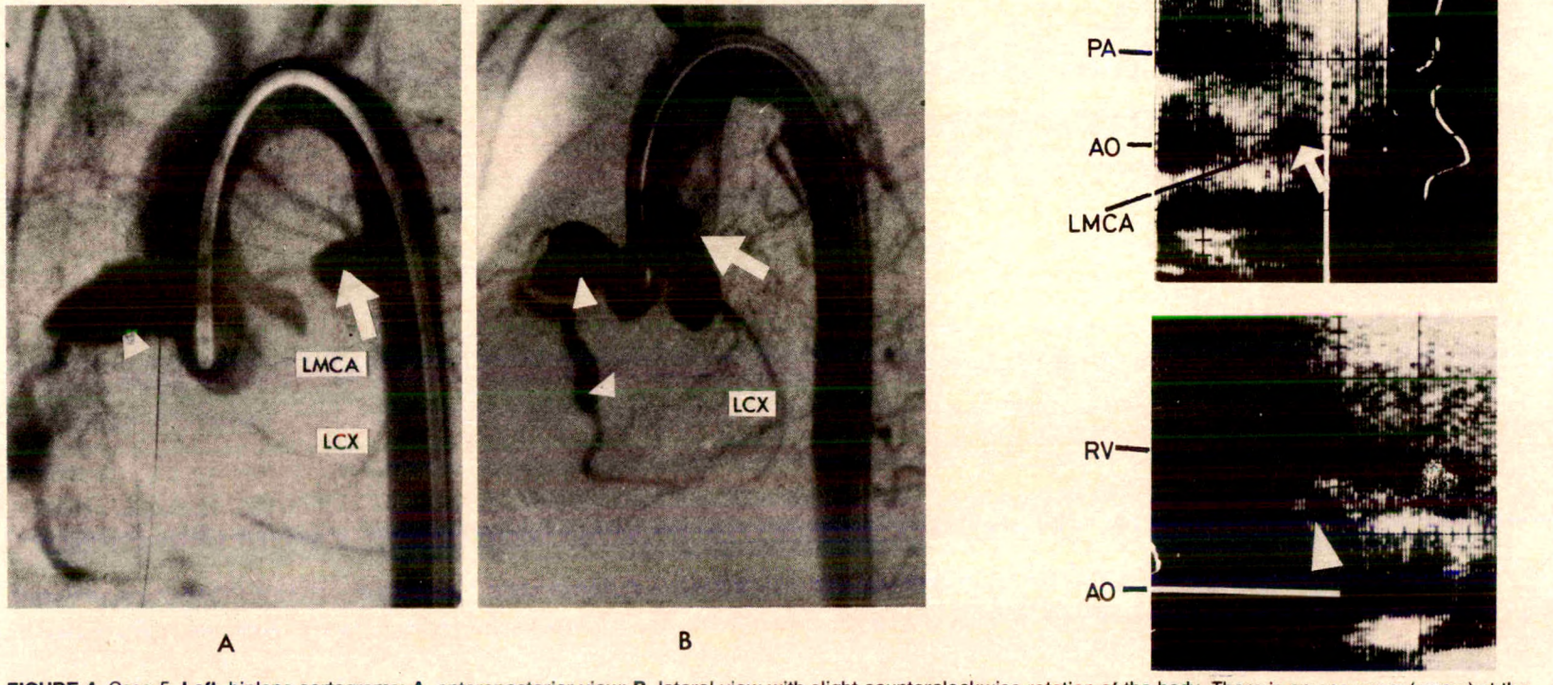


FIGURE 4. Case 5. **Left,** biplane aortograms; **A**, anteroposterior view; **B**, lateral view with slight counterclockwise rotation of the body. There is an aneurysm (**arrow**) at the bifurcation of the left main coronary artery. Moreover, an aneurysm (**arrowheads**) of the right coronary artery is seen in both views. **Right,** two dimensional echocardiogram corresponding to the left angiogram. There is a spherical echo-free space (**arrow**) representing the aneurysm in the area 1 cm distant from the ostium of the left main coronary artery (LMCA) (**above**). A spherical echo-free space (**arrowhead**) is also noted in the stem of the right coronary artery (**below**). Abbreviations as in Figure 1.

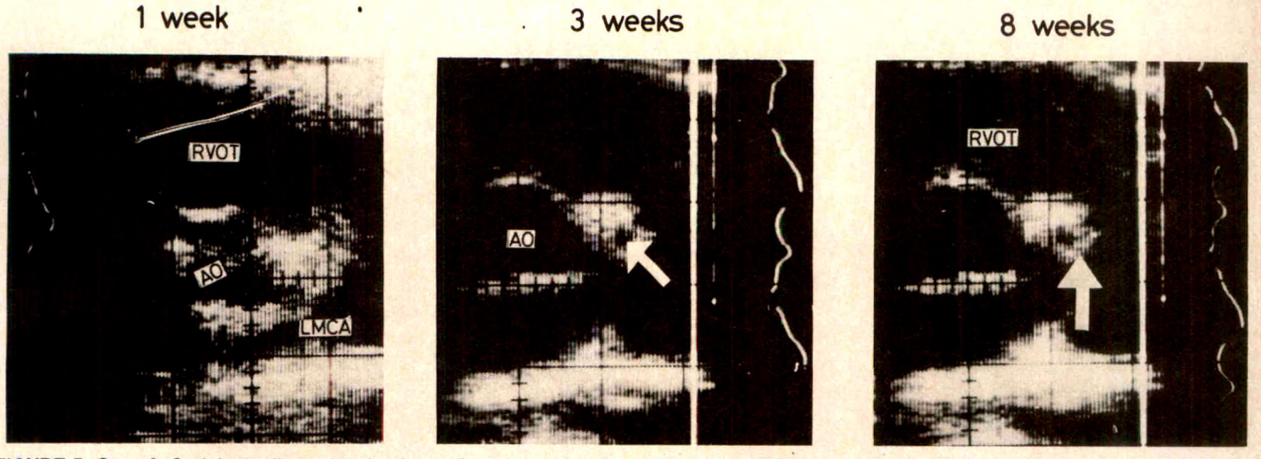


FIGURE 5. Case 6. Serial two dimensional echocardiograms during the active stage of the mucocutaneous lymph node syndrome. A spherical echo-free space (**arrow**), found in the area 3 mm distant from the ostium of the left main coronary artery (LMCA) at 3 weeks; this did not change at 8 weeks. AO = aorta; RVOT = right ventricular outflow tract.

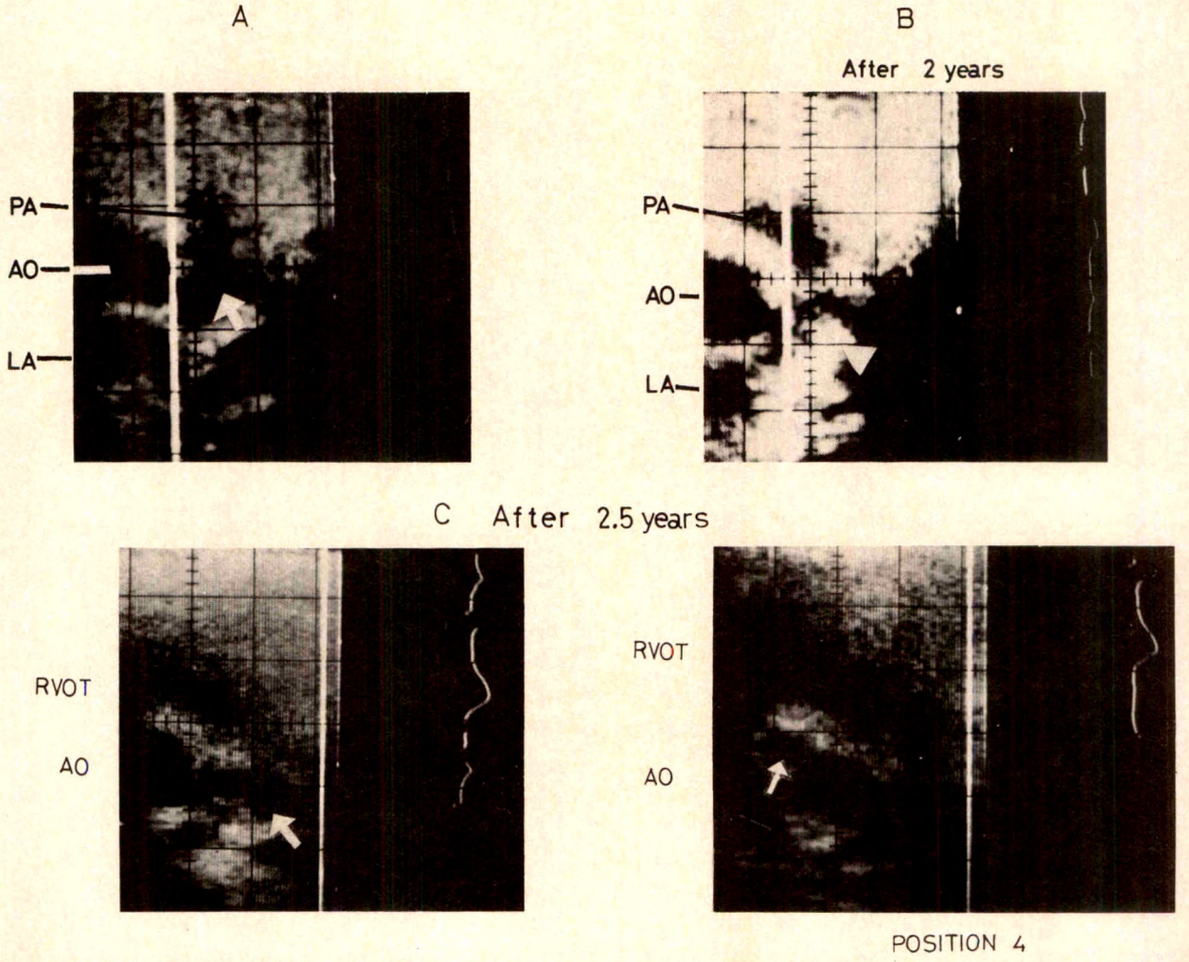


FIGURE 6. Case 2. Serial two dimensional echocardiograms. **A**, spherical echo-free space (**arrow**) is evident in the left coronary artery. **B**, an echocardiogram performed 2 years later shows a pattern suggesting the formation of thrombus (**arrowhead**) in the echo-free space. **C**, the pattern seen in **panel B** has disappeared 6 months later. The **arrow** points to the aneurysm. LA = left atrium; RVOT = right ventricular outflow tract; other abbreviations as in Figure 1.

ribs in children. In our study, the distance to display was adjusted to 5 to 7 cm because the left main coronary artery lies at a 3 to 5 cm depth in infants and young children. With such adjustment, 40 to 50 frames/sec were obtained. An image obtained with electrocardiographic gating during one cardiac cycle was adequate for analysis, and the quality was good. Resolution is described by the manufacturer of the system to be good enough for a 2 mm width and 1 mm depth of a close object. Resolution of the image seems to be adequate because a left main coronary artery with a diameter of 1 mm was detected as two straight lines, and 90 percent of the left main coronary arteries detected in our study were less than 2 mm in diameter. Therefore, it was possible to get a clear image of the left main coronary artery even in infants under age 6 months.

Problems in echocardiographic interpretation: It is important to position the probe and to direct the beam in a manner that will avoid false positive readings. When the left coronary artery is visualized, the branch of the pulmonary artery may be visualized as an echo-free space if the beam is directed too superiorly; a part of the pulmonary artery and left ventricle are also visualized if the beam is directed inferiorly from a higher intercostal space. These echo-free spaces resemble the aneurysm but, carefully judging the relations of the aorta, "mass of echoes" and echo-free space and by checking the persistence of these relations as the scanning plane changes, false positive interpretations can be avoided.

Although our study group is too small to permit evaluation of false negative results the following findings may be relevant. Because of anatomic reasons, detection of aneurysms in the left circumflex and the right coronary arteries may be difficult. The left circumflex artery turns sharply as it branches away from the left main coronary artery and is no longer in the scanning plane after this branching, and the sternum may prevent the recording of the stem of the right coronary artery. However, we were able to visualize clearly the aneurysm of the stem of the right coronary artery by changing the position of the patient and the direction of the beam (position 4).

The length of the left main coronary artery is an important factor in whether two dimensional echocardiography can detect a coronary aneurysm at its branching point or at the stem of the left anterior descending artery, the two sites where aneurysms occur most frequently in patients with the mucocutaneous lymph node syndrome.[31] Previous reports indicated that in adults the length of the left main coronary artery ranged from 4 to 15 mm (mean 10.5 mm) on angiographic study[32] and from 0 to 32 mm (mean 9.5 mm, less than 20 mm in 95 percent of patients) on pathologic study.[33] There is no report concerning the length of the left main coronary artery in children, but presumably it is correlated with age. We were able to visualize the "mass echo" surrounding the left main coronary artery for a distance of more than 8 mm in 90 percent of children. Therefore we believe that in most children it is possible to detect an aneurysm of this vessel and its branching point with the two dimensional echocardiogram. The smallest aneurysm confirmed with angiography in our study was 4 to 5 mm in diameter, but we cannot comment on determining the size from our study because of the small number of patients and variable measurement at each scan plane.

Implications: From our studies we conclude that, with careful recording and interpretation, two dimensional echocardiography is a useful and reliable method for the diagnosis and follow-up of patients with coronary arterial aneurysm.

Acknowledgment

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Addendum

Since this paper was submitted, Yoshikawa et al.[34] reported detection of aneurysms of the right as well as the left main coronary artery with two dimensional echocardiography. Our results agreed with theirs. However, we believe that the linear scan methods we used are more suitable for infants than the sector scan methods because they provide better visualization of the structures in the near field. Use of this technique in our patients and normal subjects yielded few positive results and permitted detection of the aneurysm at the bifurcation of the left main coronary artery and the stem of the left anterior descending artery.

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Sucking Action of the Left Ventricle

Demonstration of a Physiologic Principle by a Gunshot Wound Penetrating Only the Right Side of the Heart

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This report describes a man who died after a gunshot wound that entered the right atrium and exited from the right ventricle without entering the cardiac septa or the left side of the heart. At necropsy, the left atrial appendage was found to be inverted and invaginated into the mitral orifice. The invagination of the left atrial appendage is viewed as anatomic evidence that a negative left ventricular pressure was created as the left ventricular volume rapidly decreased as a result of right-sided cardiac exsanguination. Previously reported experiments in animals demonstrating the sucking (negative pressure) action of the left ventricle during ventricular diastole are summarized. The prerequisite for creation of a negative pressure in the ventricles during diastole is an extreme diminution in left ventricular volume, in this case as a result of right-sided cardiac bleeding. Only a vacuum effect of the left ventricle during diastole can explain the inversion and invagination of the left atrial appendage in this patient.

Whether the human cardiac ventricles can create a negative pressure or have a suction-like action has been debated for years. This report is the first to present evidence that the human left ventricle does have the capacity under certain circumstances to create a negative pressure and to suck blood into it from the left atrium.

Case Report

The bullet from a 0.38 caliber handgun penetrated the right side of the chest of a 27 year old man sitting in a car, killing him within minutes. At necropsy (Case 78–301), the right side of the chest contained large quantities of blood, and about 300 ml of blood was present in the pericardial sac which had been severed by the bullet at two sites (Fig. 1). The projectile had entered the heart through the right atrial appendage and exited through the right ventricular outflow tract. The bullet did not enter the left side of the heart, and both atrial and ventricular septa were intact. The left side of the heart was completely devoid of blood, and the left atrial appendage was inverted and invaginated into the mitral orifice (Fig. 1 and 2).

Comments

Spontaneous invagination of the left atrial appendage into the mitral orifice has not been described previously to our knowledge, and its explanation provides new insight into the physiologic dynamics of the human left ventricle. When the bullet perforations were made in the walls of the right atrium and ventricle, no blood thereafter entered the lungs. Tamponade was prevented because the perforations in the parietal pericardium provided egress for blood entering the pericardial sac from the right atrium and ventricle. After the cardiac wound, the only blood available to the left ventricle was that already present in the left-sided chambers and in the lungs. After emptying its chambers and the blood in the lungs, the left ventricle created a sucking action—actually

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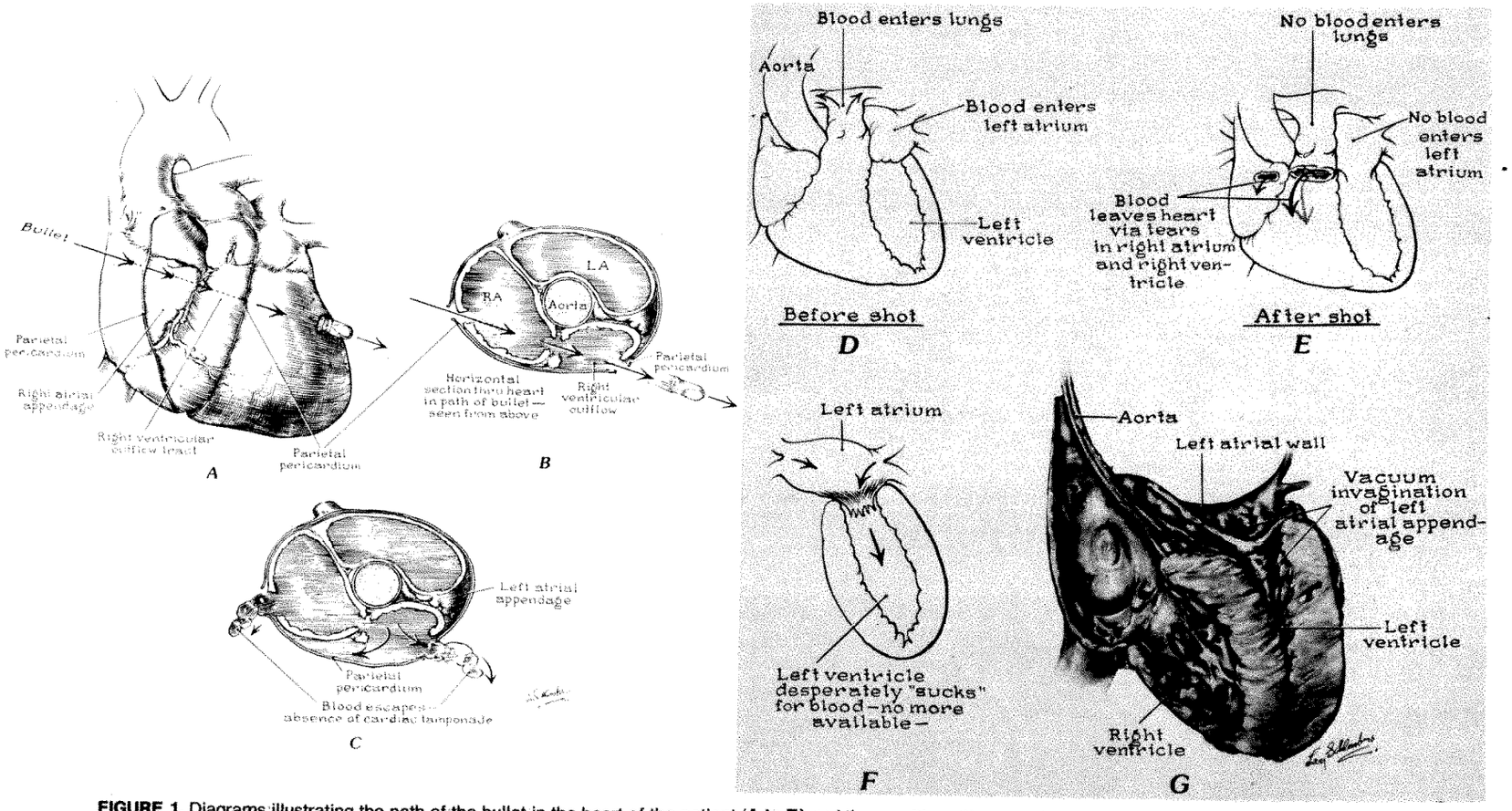


FIGURE 1. Diagrams illustrating the path of the bullet in the heart of the patient **(A to E)** and the resulting effects on the left atrium and left ventricle **(F and G).**



FIGURE 2. Opened left atrium, mitral valve and left ventricle showing the inverted left atrial appendage protruding into the mitral valve orifice.

a vacuum effect—that caused the left atrial appendage to invaginate and to be "pulled" through the mitral orifice toward the left ventricle.

For years, indeed centuries, it has been debated whether the cardiac ventricles filled entirely passively or filled to some extent by an active sucking action. In 1628, William Harvey[1] stated "... it is not true, as commonly believed, that the heart by its own action or distention draws blood into the ventricles ... blood enters the ventricles, not by the suction or dilatation of the ventricles, but by the beat of the auricles." In 1922, Wiggers and Katz[2] demonstrated that it was not atrial contraction which filled the ventricles, and in 1930 Katz,[3] utilizing the isolated turtle ventricle connected to a reservoir, demonstrated during relaxation that the pressure within the ventricle dropped below the zero level of the system, thus demonstrating that the mammalian ventricle "... can exert a sucking action ..."

Experimental demonstration of negative pressures within the ventricles: Several experimental preparations described in the 1950's demonstrated negative pressures within the cardiac ventricles.[4–10] In all of these preparations and in our patient, negative pressures were created in the ventricular cavities only when the *ventricular end-systolic volumes were extremely small.* In 1955 Bloom[4] demonstrated, with motion pictures of the excised rat heart immersed in saline solution, that the left atrial walls descended into the mitral orifice (just as in our patient) with each ventricular diastole and that fluid was ejected from the aorta with each ventricular systole. Bloom concluded that the ventricle was able to fill only because it had developed a negative pressure. In 1956, Bloom and Ferris,[5,6] using the excised beating rat heart suspended in saline solution, found that with the atria intact the ventricular pressures were continuously negative (causing the atria to collapse, as in our patient, and thus preventing inflow into the ventricles). However, when the atria were excised, the ventricular diastolic pressure was only slightly negative and the systolic pressure in the ventricles was positive. These authors also found that in the open chest intact dog the right ventricular diastolic pressure was slightly negative and became progressively more negative as the inflow (from the superior and inferior vena cava and coronary sinus) was occluded. As the venous return was progressively more occluded, the ventricular pressure tracing approached that of the excised heart with intact atria. In 1956 Brecher[7] also recorded negative (−1.3 to −10.8 cm H_2O) ventricular diastolic pressures in the intact dog heart (submerged by filling the chest with saline solution) when the mitral orifice was temporarily occluded. Ventricular diastolic pressures in some animals became more negative when epinephrine was administered. Although the mitral orifice was occluded in his experiments, saline solution or blood flowed into the ventricle through a left ventricular cannula connected to a reservoir situated below the level of the heart. He concluded that the mammalian ventricle was capable of sucking blood from the atrium into its cavity.

Using the same experimental design and the dog, Brecher and Kissen[8] showed that the negative diastolic ventricular pressure of the empty or severely volume-depleted ventricle (from manual expression of the ventricular contents) gradually rose to 0 and finally became positive as fluid was progressively added to the ventricles. An average of 5 and 8 ml of fluid had to be added to the right and left ventricles, respectively, to raise the negative ventricular pressures to 0.

Fowler and associates[9] confirmed the observation of Brecher that obstruction to left ventricular inflow (produced by inflation of the bag of a Foley catheter inserted through the left atrial appendage) did indeed result in negative (−2.5 to −18 mm Hg) left ventricular diastolic pressures; obstruction to right ventricular inflow (produced by occluding the superior and inferior vena cava and coronary sinus) caused negative (−1 to −3 mm Hg) right ventricular diastolic pressures. As Brecher[10,11] observed, negative ventricular diastolic pressure did not develop immediately upon obstruction to filling, but rather after several heart beats. This observation indicates that the negative pressure occurs only after the heart has been reduced to a critical volume by expulsion of its contents in systole.

Role of hemorrhage from right ventricle: Fowler et al.[9] produced experimentally the identical situation that occurred spontaneously in our patient, namely, the effect of rapid bleeding from the right ventricle on left ventricular diastolic pressure. Rapid exsanguination was produced by inserting a rubber tube into the right ventricular cavity, the same site of bleeding as in our patient. During removal of 360 to 700 ml of blood in 89 to 236 seconds, the left ventricular diastolic pressures fell from control levels of 0 to +5 mm Hg to −2.5 to −6.5 mm Hg.

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Fatal Acute Bacterial Myocarditis After Dentoalveolar Abscess

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A 19 year old woman presented with chest pain after a dental extraction for a dentoalveolar abscess. Electrocardiographic and serum isoenzyme changes were consistent with acute anterior myocardial infarction. At autopsy bacteria were demonstrated within the myocardium in the absence of a myocardial abscess or endocarditis. This case illustrates the occurrence of isolated acute bacterial myocarditis after a dental extraction.

Myocarditis presents as inflammatory changes within the myocardium without involvement of the valves, pericardium or other cardiac structures. Myocarditis has been documented to be secondary to bacteria, viruses and toxic agents as well as to immune response mechanisms.[1–4] The clinical presentation of myocarditis may be an arrhythmia, chest pain, fever or even sudden death or an acute myocardial infarction.[5,6]

The following case report describes a young woman who, after treatment for a dentoalveolar abscess, presented with chest pain and electrocardiographic findings of acute myocardial infarction. At necropsy there was isolated bacterial myocarditis with three distinct organisms demonstrated in the myocardium in the absence of endocarditis. This appears to be the first case of acute isolated bacterial myocarditis in which the organism was demonstrated within the myocardium.

Case Report

A 19 year old white college student was well until 12 days before admission when she sought dental attention. A dentoalveolar abscess was found and the affected tooth was extracted. She was treated with erythromycin, 250 mg four times daily, for 5 days beginning the day before extraction. She remained asymptomatic and afebrile until approximately 2 days before admission when she first noticed the onset of a sharp intermittent substernal pain that did not radiate. Mild nausea but no diaphoresis accompanied the pain. She had no cough, shortness of breath or hemoptysis. She denied any leg pain. There had been no fever or chills except for an oral temperature of 101°F noted on the day of admission. She had no previous history of chest pain, rheumatic fever, heart murmur, diabetes, hypertension or any lipid abnormality. She did not take birth control pills or immunosuppressive agents. She had no exposure to toxins or animals and had not traveled recently. The family history revealed no cardiovascular disease.

Physical examination on admission revealed a thin woman lying in bed complaining of mild substernal discomfort. The blood pressure was 92/50 mm Hg, the pulse 107/min and the temperature 102° F. The skin was cool, and there was no evidence of xanthomas or petechiae. The cardiovascular examination revealed no abnormal physical findings.

Laboratory data revealed a hemoglobin of 12.1 g/100 ml with a hematocrit of 35 percent. The white blood cell count was 12,500 mm^3 with 84 polymorpho-

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nuclear leukocytes. The sedimentation rate was 46 in 1 hour. Urinalysis was normal. Blood chemistry values were normal as were the arterial blood gases on room air. Serum creatine kinase (CK) on day 1 was 520 units and 1,420 units on day 2. CK MB and MM isoenzyme levels were elevated on both days 1 and 2. Lactic dehydrogenose (LDH) was 374 units on day 1 and 507 units on day 2. LDH-2 was greater than LDH-1 on both days 1 and 2.

The electrocardiogram on admission (Fig. 1) revealed sinus tachycardia with low voltage. Hyperacute S-T segment elevations in the anterior precordial leads were consistent with acute anterior wall myocardial infarction. Minor S-T segment elevation was also noted in lead II. The chest X-ray film revealed a normal heart size and pulmonary vascular pattern.

Hospital Course

The patient presented with chest pain. Electrocardiographic and laboratory findings were consistent with an acute anterior wall myocardial infarction. A temperature of 101°F was present on admission, and three blood cultures were obtained. A rare episode of substernal pain occurred during the first few hours of admission and was relieved with nitroglycerin. Occasional premature ventricular complexes were noted and lidocaine infusion was instituted. An echocardiographic study revealed no evidence of valve disease or vegetations. No mitral valve prolapse or myxoma was noted. Septal and posterior wall thickness was normal, but excursion was diminished. There was no pericardial effusion.

Approximately 10 hours after admission the blood pressure decreased to 70/40 mm Hg. A Swan-Ganz catheter revealed a right ventricular pressure of 9/0, a pulmonary arterial pressure of 9/1 and a pulmonary capillary wedge mean pressure of 1 to 2 mm Hg. After therapy with fluid replacement, the blood pressure increased to 88/60 mm Hg but decreased again to 60/40 mm Hg despite increased fluid administration. The pulmonary capillary wedge pressure increased to 22 mm Hg and dopamine infusion and digitalization were then instituted. The patient remained hypotensive with an elevated pulmonary capillary wedge pressure. While preparation was undertaken for intraortic balloon counterpulsation, ventricular irritability with recurrent periods of ventricular tachycardia developed. These episodes were unresponsive to defibrillation and antiarrhythmic therapy, and the patient died 20 hours after admission. The following day, two of three blood cultures drawn at the time of admission were positive for the following organisms: alpha hemolytic streptococcus group D, alpha hemolytic streptococcus not group D, veillonella species, hemophilus parainfluenza and diphtheroid bacilli.

Postmortem Examination

Autopsy was performed 2 hours after the patient's death. The pathologic findings were limited to the heart. The heart weighed 220 g and showed mild dilatation of all cardiac chambers. No cardiac hypertrophy was noted. The myocardium was soft to slightly firm, showing multiple focal areas of reddish-brown to slightly yellowish discoloration in the myocardium of all chambers. The cardiac valves were carefully examined and did not reveal vegetations or evidence of endocarditis. The subvalve apparatus was not abnormal. No patent foramen ovale or congenital anomalies were noted. The coronary arteries were patent throughout their course and revealed no significant atherosclerotic lesions and no thromboemboli in the lumen. No coronary dissection or aberrant coronary artery was identified. Myocardial abscesses were not present.

On microscopic examination, there were multiple disseminated foci of myocardial necrosis with eosinophilia and loss of cross striations in both the ventricular and the atrial myocardium. The areas of necrosis were infiltrated predominantly by lymphocytes and of lesser number of polymor-

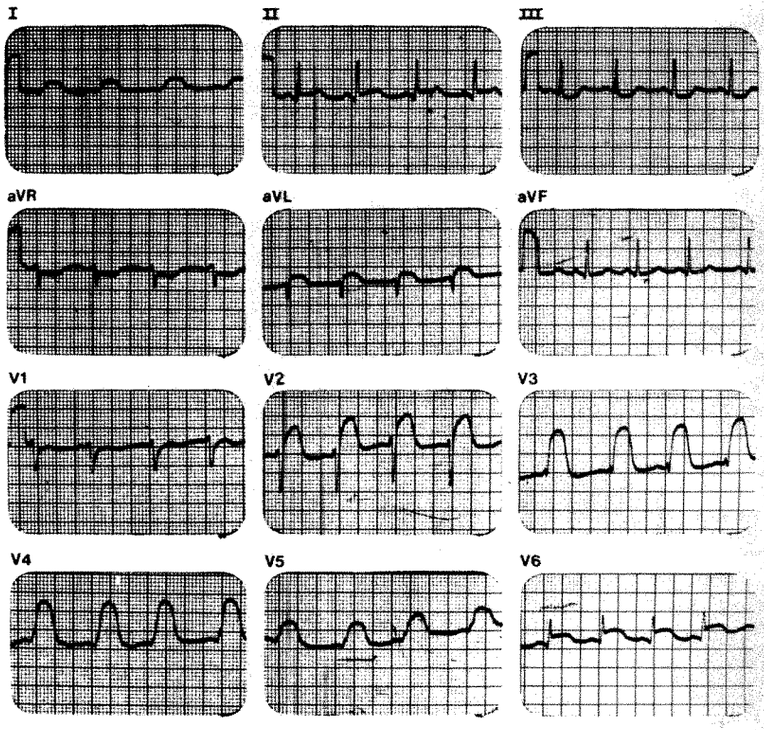
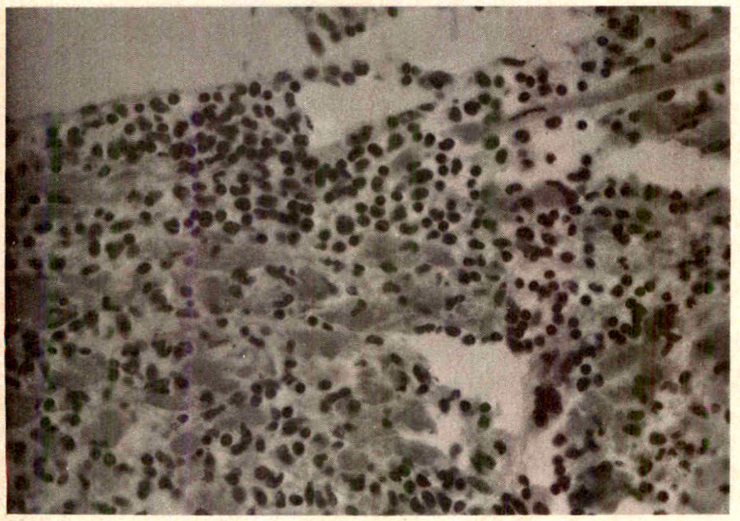
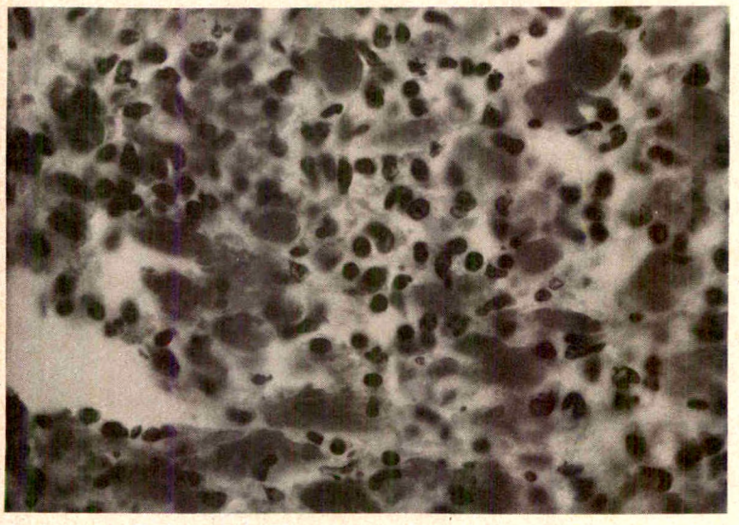


FIGURE 1. Admission electrocardiogram.





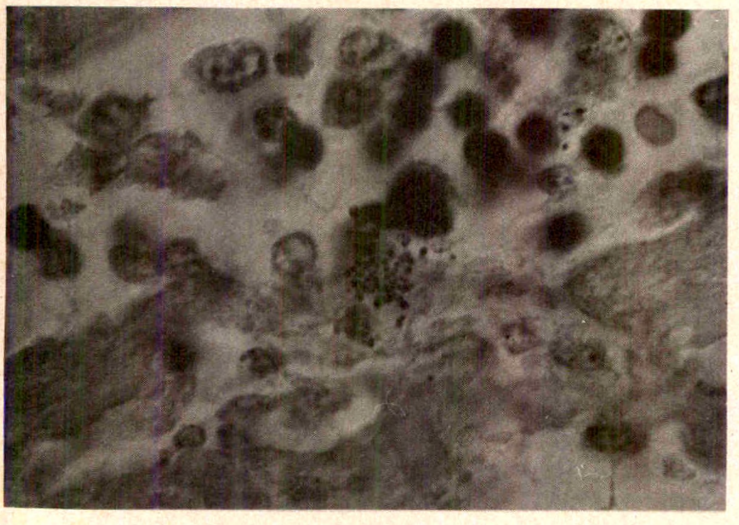


FIGURE 2. Photomicrographs. **Top and center,** hematoxylin-eosin stains showing myocardial necrosis infiltrated predominantly by lymphocytes and a lesser number of polymorphonuclear leukocytes, macrophages and occasional plasma cells. **Bottom,** Brown and Brenn stain of the myocardium showing gram positive and gram negative cocci. **Top** X200, **center** X400, **bottom** X1,000, all reduced by 58 percent.

phonuclear leukocytes, macrophages and occasional plasma cells. (Fig. 2 (top and center)). Brown and Brenn bacterial stain on the sections of the heart revealed the presence of gram positive and gram negative cocci and occasional gram negative bacilli (Fig. 2, bottom). The remaining autopsy findings were essentially normal. There was no evidence of pyogenic foci or of infection in other organs of the body, including the lungs, liver, spleen, genitourinary tract and brain. Brown and Brenn stain of the lungs, liver, kidneys and brain did not demonstrate bacteria. The site of the dental extraction was well healed, and no evidence of abscess was seen.

Discussion

The clinical presentation of myocarditis is varied. Our patient presented with the clinical features of acute myocardial infarction with characteristic electrocardiographic and serum isoenzyme changes, followed by cardiogenic shock. The possible causes considered for infarction were coronary embolization, an aberrant coronary artery or primary coronary arterial dissection.

The sequence of events in this patient merit comment. Despite a brief course of antibiotic therapy bacteria occurred in the bloodstream with isolated involvement of the myocardium. The organisms cultured from the blood of this patient before death can be found as normal flora in the oral cavity and upper respiratory tract. At necropsy there was no evidence of endocarditis, and no bacteria were demonstrated in any of the other organs. It therefore appears that bacteria originating in the oral cavity resulted only in isolated involvement of the myocardium. Because isolated bacterial myocarditis is extremely rare the possibility of an immunosuppressed host was considered. However, the clinical findings did not indicate recurrent infections, and the patient was not taking immunosuppressive agents.

Myocarditis in association with nasopharyngeal infection has previously been described,[7,8] but in the reported studies, histologic sections did not reveal the presence of bacteria. The histologic sections in our case revealed the presence of multiple disseminated patchy areas of inflammation and necrosis with demonstrable gram positive and gram negative organisms. These findings are indicative of acute bacterial myocarditis. We believe that these bacteria are representative of those bacteria cultured in the antemortem blood. It should be noted that the myocardium in our patient was the sole site of the pathologic process, and there was no involvement of the cardiac valves, pericardium or other organs of the body.

In summary, this case demonstrates the need to suspect myocarditis in young persons who present with clinical signs of myocardial infarction. Acute bacterial myocarditis as well as endocarditis should be considered in patients who present with fever and chest pain after a dental procedure.

Acknowledgment

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Hypertrophic Cardiomyopathy: A Discussion of Nomenclature*

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In 1958, Teare[1] presented the first systematic description of cardiac disease characterized by "asymmetrical hypertrophy of the heart" and nondilated ventricular cavities. His observations were based on postmortem examination of eight patients, seven of whom had died suddenly. Subsequent investigations led to a dramatic evolution of the concepts concerning the clinical and pathophysiologic spectrum of this disease which, in the process, has acquired no fewer than 58 names (Table I). The fact that this dubious distinction has caused considerable confusion over the years[2,3] has prompted us to review briefly the derivation of the more widely used names in the hope that a commonly acceptable standard nomenclature may eventually be adopted. As will become clear in the ensuing discussion, the name we now prefer for this disease is hypertrophic cardiomyopathy. This term, as it is used here, refers to a primary disease of cardiac muscle and excludes by definition all secondary systemic diseases that cause increased cardiac mass.

The multiplicity of descriptive names given to this disease reflects primarily two facts. First, several centers were involved more or less simultaneously in the pioneering studies that characterized the disease and each, understandably, developed names for this newly discovered clinical entity based on those aspects of the disease that were most impressive to the individual investigator. Second, as additional information accumulated, concepts of the disease changed, with important new insights often leading to new names.

Asymmetric septal hypertrophy: In the first 15 years after Teare's initial report, the majority of terms used to describe hypertrophic cardiomyopathy emphasized left ventricular outflow obstruction, a finding that was thought to be highly characteristic of this disease. Thus, the terms idiopathic hypertrophic subaortic stenosis,[4,5] hypertrophic obstructive cardiomyopathy[6] and muscular subaortic stenosis[7] became widely used. The widespread application of echocardiography to cardiac diagnosis in the early 1970's confirmed the hypertrophic nature of the disease[8–10]; it also (1) demonstrated that no outflow obstruction was present in a large proportion of patients,[11] and (2) appeared to show that a hypertrophied ventricular septum measuring at least 1.3 times the thickness of the left ventricular free wall was invariable.[8] Furthermore, in the vast majority of patients, about one half of the first degree relatives of patients with hypertrophic cardiomyopathy also showed an abnormal septal-free wall thickness ratio with echocardiography.[11,12] These echocardiographic observations led (1) to the introduction of the term "asymmetric septal hypertrophy" and its acronym "ASH" to describe the *disease* hypertrophic cardiomyopathy,[8] and (2) to the concept that asymmetric septal hypertrophy was genetically transmitted as an autosomal dominant trait.

However, it soon became evident that asymmetric septal hypertrophy was *not* pathognomonic of hypertrophic cardiomyopathy. Specifically, our echocardiographic and necropsy studies[13–15] conducted over the past 3 years in more than 500 patients revealed that ventricular septal thickening and a septal-free wall thickness ratio of 1.3 or more was present in about 10 percent of patients with a variety of congenital or acquired heart diseases. When such an abnormal septal-free wall ratio occurred in these patients, the septal thickening was usually secondary to the patient's underlying lesion and not a manifestation of a coexistent primary cardiomyopathy.[13–16]

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Because the term asymmetric septal hypertrophy had already been appropriated for the name of the primary cardiomyopathy, these findings led to yet another dilemma in nomenclature—how to refer to the type of disproportionate septal thickening that occurred secondary to other types of heart disease. Hence, the descriptive term "disproportionate septal thickening," or "DST," was introduced[13–16] to describe the secondary form of asymmetric septal hypertrophy. Although the acronyms ASH and DST were thus used to describe the *same gross anatomic abnormality* (a hypertrophied ventricular septum that was at least 1.3 times the thickness of the left ventricular free wall), each term had a very different meaning. ASH implied the existence of a primary cardiomyopathy; DST implied a secondary form of disproportionate ventricular septal thickening.

Hypertrophic cardiomyopathy without asymmetric septal hypertrophy: Two other observations added to this confusion. First, it became evident that not all patients with hypertrophic cardiomyopathy had asymmetric septal hypertrophy.[17–19] For example, an occasional patient has been identified with concentric (symmetric) ventricular hypertrophy and nondilated ventricular cavities whose family members had typical hypertrophic cardiomyopathy with a septal-free wall ratio of 1.3 or more.[17] Second, in some patients with cardiomyopathy and concentrically hypertrophied nondilated hearts, genetic transmission could not be documented.[17] Although these latter patients could have genetically transmitted hypertrophic cardiomyopathy (but with incomplete penetrance), these findings raise the possibility that another form of hypertrophic cardiomyopathy exists that is not genetically transmitted and is not characterized by asymmetric septal hypertrophy. Of course, the M mode ultrasonic beam is discrete and provides an assessment of only a small portion of ventricular septum and the posterobasal segment of the left ventricular free wall. It is therefore possible that forms of hypertrophic cardiomyopathy may be described in which there is asymmetric thickening of the left ventricle involving primarily the anterior or lateral segments of the left ventricular free wall rather than the septum.

Hypertrophic cardiomyopathy—the preferred name?: Hence, the reasons for the application of numerous names to this primary cardiomyopathy, and the subsequent confusion as to what disease is actually being referred to, are readily understandable. Nonetheless, it would now seem appropriate to choose a name that is both acceptable to the majority of students of this entity and consistent with its most characteristic features. Because (1) an abnormal septal-free wall thickness ratio is not an invariable feature of hypertrophic cardiomyopathy, and (2) disproportionate septal thickening commonly occurs as a consequence of other diseases, ASH appears to be a less attractive name for the *disease entity* than we originally thought. The same argument applies to names emphasizing obstruction to left ventricular outflow, because obstruction is absent in a large proportion of patients. Because the single most consistent and characteristic feature is a hypertrophied heart (that is, one having increased cardiac mass), with a nondilated left ventricular cavity in the absence of a cardiac or systemic disease that itself could produce left ventricular hypertrophy, we believe it is most reasonable to refer to this disease as *hypertrophic cardiomyopathy*. This is a name developed and used for many years by our colleagues in the United Kingdom,[20–22] and for which they deserve full credit. However, we should also point out that even this definition

TABLE I

Terms Used to Describe Hypertrophic Cardiomyopathy

Asymmetrical hypertrophic cardiomyopathy	1972*
Asymmetrical hypertrophy of the heart	1958
Asymmetrical septal hypertrophy	1973
Brock's disease	1977
Diffuse muscular subaortic stenosis	1973
Diffuse subvalvular aortic stenosis	1961
Dynamic hypertrophic subaortic stenosis	1971
Dynamic muscular subaortic stenosis	1966
Familial hypertrophic subaortic stenosis	1961
Familiar muscular subaortic stenosis	1959
Familiar myocardial disease	1967
Functional aortic stenosis	1959
Functional hypertrophic subaortic stenosis	1969
Functional obstructive cardiomyopathy	1973
Functional obstruction of the left ventricle	1957
Functional obstructive subvalvular aortic stenosis	1968
Functional subaortic stenosis	1960
Hereditary cardiovascular dysplasia	1961
Hypertrophic cardiomyopathy	1970
Hypertrophic constrictive cardiomyopathy	1972
Hypertrophic hyperkinetic cardiomyopathy	1965
Hypertrophic infundibular aortic stenosis	1971
Hypertrophic nonobstructive cardiomyopathy	1975
Hypertrophic obstructive cardiomyopathy	1964
Hypertrophic stenosing cardiomyopathy	1972
Hypertrophic subaortic stenosis	1962
Idiopathic hypertrophic cardiomyopathy	1972
Idiopathic hypertrophic obstructive cardiomyopathy	1966
Idiopathic hypertrophic subaortic stenosis	1960
Idiopathic hypertrophic subvalvular stenosis	1966
Idiopathic muscular hypertrophic subaortic stenosis	1966
Idiopathic muscular stenosis of the left ventricle	1969
Idiopathic myocardial hypertrophy	1963
Idiopathic stenosis of the flushing chamber of the left ventricle	1964
Idiopathic ventricular septal hypertrophy	1962
Irregular hypertrophic cardiomyopathy	1968
Left ventricular muscular stenosis	1968
Low subvalvular aortic stenosis	1962
Muscular aortic stenosis	1969
Muscular hypertrophic stenosis of the left ventricle	1966
Muscular stenosis of the left ventricle	1961
Muscular subaortic stenosis	1966
Muscular subvalvular aortic stenosis	1964
Non-dilated cardiomyopathy	1974
Nonobstructive hypertrophic cardiomyopathy	1975
Obstructive cardiomyopathy	1960
Obstructive hypertrophic aortic stenosis	1967
Obstructive hypertrophic cardiomyopathy	1968
Obstructive hypertrophic myocardiopathy	1968
Obstructive myocardiopathy	1968
Pseudoartic stenosis	1958
Stenosing hypertrophy of the left ventricle	1966
Stenosis of the ejection chamber of the left ventricle	1966
Subaortic hypertrophic stenosis	1964
Subaortic idiopathic stenosis	1968
Subaortic muscular stenosis	1964
Subvalvular aortic stenosis of the muscular type	1962
Teare's disease	1977

* Dates indicate the year that the term was first published.

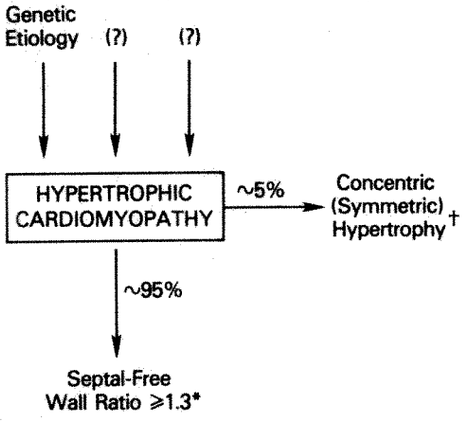


FIGURE 1. Spectrum of hypertrophic cardiomyopathy; *associated with absolute ventricular septal thickening (usually 15 or more mm in the adult); †ventricular septal to left ventricular free wall thickness ratio less than 1.3.

has its exceptions because some patients with "end stage" hypertrophic cardiomyopathy may actually have left ventricular dilatation.[23]

Nevertheless, we continue to find it convenient and useful to employ the acronym ASH to describe specifically the asymmetrically thickened ventricular septum present in patients with hypertrophic cardiomyopathy and the term disproportionate septal thickening (or DST) to refer to the same gross anatomic abnormality when present in patients with other forms of heart disease. However, we are aware that there is a redundancy in these two terms and that the distinction between them may often appear ambiguous.

Finally, we are also cognizant that hypertrophic cardiomyopathy may ultimately prove not to be a single etiologically distinct disease entity (Fig. 1). This situation could induce a confrontation between those semanticists who prefer to "split" and those who prefer to "lump." The former might favor applying different names to the condition of patients having hypertrophic cardiomyopathy with a septal-free wall ratio of 1.3 or more and to that of patients with concentric hypertrophy; another term could be found to describe the findings in patients with an obvious genetic disease, and yet another for those in whom a genetic etiology is equivocal or absent. However, it has still not been established with certainty whether these clinical states represent etiologically distinct diseases or different expressions of the same disease. Until more definitive evidence evolves regarding etiology and pathogenesis, we suggest that all forms of nondilated hypertrophic cardiomyopathies be termed "hypertrophic cardiomyopathy," with the understanding that a further modification of terminology may be necessary later.

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Variant Angina: More Variants of the Variant*

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As experience increases with "variant" angina, originally described by Prinzmetal et al.,[1] it becomes more difficult to define this condition as a single clinical entity. Probably the best overall operational definition is that of angina associated with S-T segment elevations not precipitated by any increase in myocardial metabolic demands. However, it may occur in patients with coronary artery disease and coexistent exertional angina, and on occasion may be provoked by exercise or occur at rest.[2,2a] Furthermore, an occasional patient whose pattern otherwise fits that of variant angina will demonstrate during pain S-T segment depressions rather than elevations. The clinical course may vary from a prolonged, relatively stable pattern to a rapidly progressive pattern with severe arrhythmias, myocardial infarction and death. Although Prinzmetal et al.,[1] in their original description, differentiated "variant" angina from "unstable" or "preinfarctional" angina by its more benign clinical course, many of their patients and those reported on later experienced myocardial infarction or death in a relatively short period of time. Like the clinical course, the anatomic substrate of variant angina varies markedly, some patients having angiographically normal coronary arteries and others having mild to moderate coronary arterial disease or severe fixed stenoses.

Coronary Spasm in Variant Angina

Coronary spasm has been established with angiography as a cause of variant angina in many patients with normal coronary arteries or hemodynamically insignificant coronary lesions. The role of spasm in patients with significant fixed obstructions is less clear, although very limited experience with ergonovine provocation[2a,3] suggests that episodes of severe spasm in the region of such lesions may be involved in precipitating ischemia in these patients also. Another interesting although untested speculation is that platelet aggregates may play a role either primarily, possibly with subsequent spasm, as a result of release of platelet vasoactive substances, or secondary to hypoxia occurring after spasm. The occasional occurrence of angina with S-T elevations during angiography without demonstrable spasm suggests the possibility of such an alternative mechanism. Whatever the mechanism, experimental animal studies[4] suggest that S-T elevations are caused by the presence of more severe transmural ischemia, and the severity of the pain and associated arrhythmias and severe perfusion defects demonstrated by thallium-201 imaging[2a] during episodes of variant angina indicate that this is true. However, in this issue of the Journal Robertson et al.,[5] like Guazzi et al.[6] in an earlier study, demonstrate that monitoring of patients with variant angina may show S-T elevations in the absence of symptoms; the significance of these painless changes is uncertain, although they may represent ischemic periods of insufficient duration to result in pain. Further confusion in definition arises from the observation that severe spasm may be accompanied only by S-T depressions or by a pseudonormalization of T wave inversions.[2a]

The Autonomic Nervous System and Coronary Spasm

When coronary spasm occurs, the autonomic nervous system appears to be involved in some way. Episodes of variant angina have been provoked in susceptible patients with administration of epinephrine alone or in combination with beta blockade with propranolol and with parasympathomimetic stimulation using methacholine.[7-9] However, we do not know how autonomic

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nervous system activity causes coronary spasm. Alternative explanations are (1) an increase in circulating catecholamines, (2) an increase in activation of the sympathetic innervation of the coronary arteries, and (3) changes in the coronary vessel walls themselves.

States such as physical exertion and emotional stress that result in an outpouring of catecholamines rarely result in episodes of variant angina. Robertson et al.[5] present evidence that their patients with variant angina did not have a generalized increase in sympathetic outflow. Biochemical measurements of sympathetic activity (circulating norepinephrine, epinephrine, dopamine, urinary catecholamines, metanephrine, normetanephrine, vanillylmandelic acid, urinary-hydroxyindole acetic acid, plasma renin activity, thyroxin and 2,3-diphosphoglycerate) were all found to be within normal limits between and, in a few instances, during episodes of variant angina. In addition, tests of sympathetic functional integrity were normal, leading to the hypothesis that the vessel wall is primarily responsible for spasm independent of central sympathetic outflow. However, the tests used (venous reflex, exercise testing, cold pressor test, handgrip, orthostasis and the Valsalva maneuver) may not necessarily reflect specific changes in cardiac innervation.

Alterations in Alpha Adrenergic System and Coronary Spasm

Also in this issue of the Journal, Ricci et al.[10] propose that the ability of phentolamine and phenoxybenzamine to abolish spasm is evidence that a pathologic alteration in the alpha adrenergic system is responsible for the spasm. On the basis of limited studies of innervated and denervated hearts, they believe that this action is secondary to stimulation of the alpha adrenergic coronary innervation.[11] However, other studies on the peripheral circulation suggest that the predominant effect of phentolamine is direct vasodilatation,[12] and thus the primary abnormality could still represent an intrinsic hyperreactivity of the vessel wall. The ability of ergonovine to provoke spasm in patients with variant angina also is not helpful in elucidating the mechanism involved, because the relative effects of this drug on the vessel wall directly and on sympathetic innervation are not known. Furthermore, although the alpha adrenergic system is probably involved in the development of spasm, the abolition of spasm by alpha blocking drugs does not necessarily indicate that excessive alpha stimulation is the primary cause of spasm occurring spontaneously.

The cyclic nature of clinical episodes of variant angina is well known. Even the ability to induce spasm by sympathetic nervous system stimulation in patients with variant angina is inconstant, and induction of spasm by epinephrine and propranolol may be possible only when spontaneous episodes of pain are occurring.[7] This view is in agreement with the concept that some cyclic variation in sympathetic tone underlies the ability of a given stimulus to induce spasm.

Ricci et al.[10] present the interesting hypothesis that patients with variant angina have a state of adrenergic imbalance, possibly at the hypothalamic level, resulting in asymmetric stellate ganglion activation at rest that, during bursts of sympathomimetic activity, results in excessive unilateral stellate ganglion discharge along cardiac nerves and selective coronary arterial spasm. This viewpoint is supported primarily by the appearance of T wave abnormalities during pain-free intervals in patients with variant angina that were normalized with isoproterenol in one patient and with phenoxybenzamine in four patients, as well as by the observation of Q-T interval prolongation immediately before episodes of coronary spasm. The T wave changes and their pharmacologic responses were analogous to those seen after unilateral stellate stimulation in animal models.[13] However, many patients with variant angina, particularly those with normal coronary arteries, do not have T wave abnormalities at rest. The Q-T interval prolongation also is similar to that seen with right stellate ganglionectomy or left stellate stimulation in animals.[13] Although this change could be considered a manifestation of ischemia, this possibility appears unlikely because the change was seen before any S-T segment shift. Q-T interval prolongation was not observed by Curry et al.,[3] indicating that this mechanism also does not universally apply. Direct measurement of cardiac nerve activity during spasm, although difficult to obtain, would be important in determining the origin of the spasm.

Ergonovine and Coronary Spasm

The use of ergonovine to provoke spasm has provided much useful information. A positive ergonovine test (severe coronary spasm demonstrated angiographically in association with chest pain and S-T elevation) appears to be quite specific for variant angina, being absent in patients with normal coronary arteries and symptoms not typical for angina. Rarely, however, a patient with significant coronary artery disease and classic angina without S-T segment shifts may also have a positive test.[3] This test also appears to be highly sensitive for variant angina although in a few reported cases with typical findings the spasm could not be provoked.[14,15] The limited evidence now available suggests that the spasm occurring after ergonovine resembles that occurring spontaneously,[3,15,16] although the severity of the spasm and its localization and extent along the vessel involved may vary with time in either spontaneous or induced spasm, and more experience is required before definite conclusions can be made.

Treatment of Variant Angina

The therapeutic decision in patients with variant angina is a difficult one. It is generally agreed that medical treatment, primarily with nitroglycerin and long-acting nitrates, is the initial therapy of choice, although such treatment may not be effective. The beneficial effect of phenoxybenzamine in a previously described patient[7] and in the few patients reported on by Ricci et al.[10] is impressive and warrants further investigation. Responses have also been reported to treatment with nylidrin and other peripheral vasodilators,[1]

reserpine, atropine,[7] propranolol[17] and, more recently, with verapamil[18] and nifedipine,[19] both coronary vasodilators and blockers of cell uptake of calcium.

Although it was initially believed that patients with variant angina fared poorly with coronary arterial surgery, there is now sufficient evidence that those who have significant fixed coronary lesions can respond well to saphenous vein coronary bypass surgery.[20,21] The decision is more difficult in patients without significant coronary lesions. Many will respond to medical treatment or their condition will improve spontaneously with time; others will continue to experience severe ischemic episodes unresponsive to treatment. Although attempts at coronary bypass surgery in these patients have been unsuccessful in a few reported cases,[22] possibly because of the recurrence of diffuse and variable areas of spasm, a few surgical successes in this situation have now been reported.[23,24] However, this remains a very uncertain means of treatment.

Attempts have been made to differentiate patients with variant angina who do or do not have significant fixed coronary obstructions on the basis of clinical presentation.[25,26] Although these classifications may be generally helpful, the overlap is too great and the exceptions too frequent for them to be useful in treating the individual patient. Because of the serious prognosis in patients presenting with angina at rest with S-T elevations and because of their different responses to treatment, it is important to differentiate between subgroups with normal and abnormal coronary arteries. It is therefore advisable to use coronary angiography early in the course of these patients. Therapeutic decisions can then be based on an angiographic as well as clinical classification. On the basis of present knowledge, it seems unlikely that all "variant angina" can be considered a single entity, and much remains to be learned about its various subgroups and their different pathophysiology and response to therapy.

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What does this hard driving magazine editor have in common



with this chronically fatigued grandmother?

Potassium depletion.

The editor's hypertension is treated with diuretics, and all effective diuretics cause kaliuresis.[1–8] Even potassium-sparing diuretics, at least when combined with thiazides, may not protect the patient from potassium losses.[1,2] Unless she eats the foods it takes to replace the losses,[3] her deficit can only grow. Those foods contain an extra 700 or 800 calories.

The grandmother's malaise and muscle weakness can be early signs of potassium deficit,[4] which can accrue from inadequate diet,[9] particularly one high in carbohydrates;[1] purgative habits;[1,5,6,9] or corticosteroid therapy.[1,4–7]

Effective potassium supplementation is required.

Both the editor and grandmother have a need for potassium. Yet safe and effective supplementation must be tailored to their individual life-styles. Patient compliance to potassium therapy can help assure a high rate of efficacy, and compliance is enhanced by dosage simplicity, convenience and taste. The woman with great demands on her time can appreciate the convenience of once-a-day dosage for her potassium needs . . . dosage that fits in with her other medication schedules. The grandmother needs an easy-to-take, good-tasting dosage form with GI safety.





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Safe and effective potassium supplementation meeting a variety of patient needs

Prescribing Considerations

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Contraindications: Impaired renal function with oliguria or azotemia; Addison's disease; hyperkalemia from any cause.

Warnings and Precautions: Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be administered with caution, and dosages adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal kidney function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Frequent checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also be directed toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients and such patients should be monitored by ECG for cardiac irregularities. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, **patients should be carefully directed to dissolve each dose completely in the stated amount of water.**

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts.

Dosage and Administration: Adults: 1 K-LYTE DS tablet (50 mEq potassium) completely dissolved in 6 to 8 ounces of cold or ice water, 1 to 2 times daily; 1 K-LYTE tablet (25 mEq potassium) completely dissolved in 3 to 4 ounces of cold or ice water, 2 to 4 times daily; 1 K-LYTE/CL tablet (25 mEq potassium chloride) completely dissolved in 3 to 4 ounces of cold or ice water, 2 to 4 times daily. **NOTE: It is suggested that K-LYTE DS, K-LYTE and K-LYTE/CL be taken with meals and sipped slowly over a 5 to 10 minute period.**

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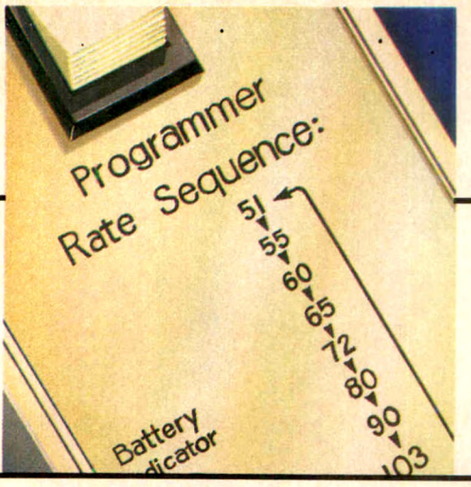
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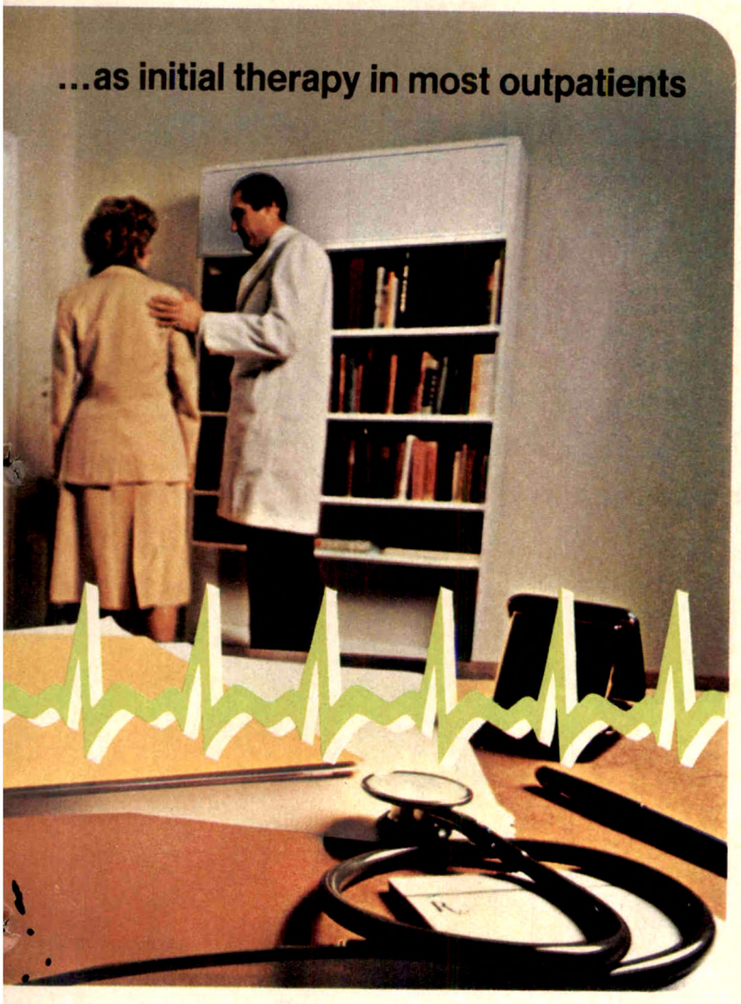
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Demonstrated efficacy

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...as initial therapy in most outpatients



More favorable side-effects profile

When compared with quinidine sulfate, Norpace is notable for its lower incidence of severe side effects. These are mainly anticholinergic in nature, are usually mild and generally transient. If urinary hesitancy or other genitourinary side effects occur, they are often dose related and frequently may be managed by downward titration of the dose of Norpace. Urinary retention, however, may occasionally occur, particularly in the older patient. Males with benign prostatic hypertrophy are at particular risk.

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Lower dropout rate than quinidine

Efficacy of Norpace, coupled with its low incidence of severe side effects, can mean significantly fewer dropouts among your dysrhythmic patients. In a clinical study involving 62 patients in each treatment group, only 8.1% of patients discontinued Norpace therapy, as compared with 35.5% who discontinued quinidine.

High level of compliance

Even the best medication may not be taken as prescribed if it causes problems for the patient. With Norpace you are prescribing not only an effective medication, but you are prescribing one you can be reasonably confident the patient will take in accordance with your instructions.

Important considerations when prescribing Norpace (disopyramide phosphate)

Patients with compromised cardiac function due to any cause may experience either hypotension or a worsening of cardiac decompensation when taking drugs with negative inotropic effects, and the physician should be aware of this possibility with Norpace. Since Norpace is primarily excreted by the kidney, patients with renal impairment will require a reduced dosage due to prolongation of the effective half-life.

The dosage of Norpace should be individualized for each patient, and the Complete Prescribing Information consulted before prescribing. Special attention to the sections on *Clinical Pharmacology, Warnings,* and *Precautions* will be helpful in determining the proper dosage, particularly for the more complex patient.

Conclusion: Norpace represents a logical choice for both initial and maintenance therapy either in hospitalized patients or in outpatients.

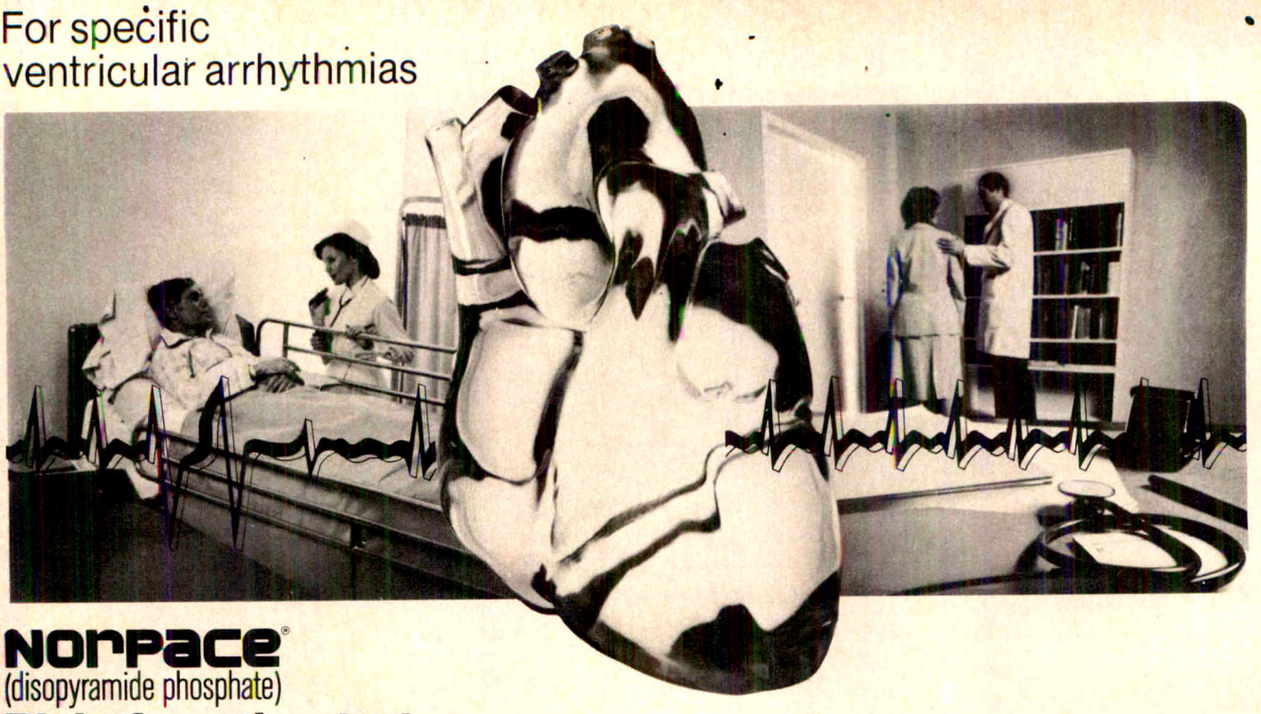
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For specific ventricular arrhythmias



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Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:

Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In patients with marginally compensated heart failure or with a history of heart failure, Norpace may worsen cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained. Patients receiving concomitant therapy with more than one antiarrhythmic drug must be carefully monitored for serious negative inotropic effects or excessively prolonged conduction, evidenced by widening of the QRS complex and/or prolongation of the Q-T interval.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace.

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *General:* nervousness, dizziness, general fatigue/muscle weakness, headache, malaise. *Cardiovascular:* hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. *Dermatologic:* generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, dysuria, and hypoglycemia (usually in patients with impaired liver function). Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.

If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

See current complete prescribing information for dosage recommendations.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100 and 500 capsules.

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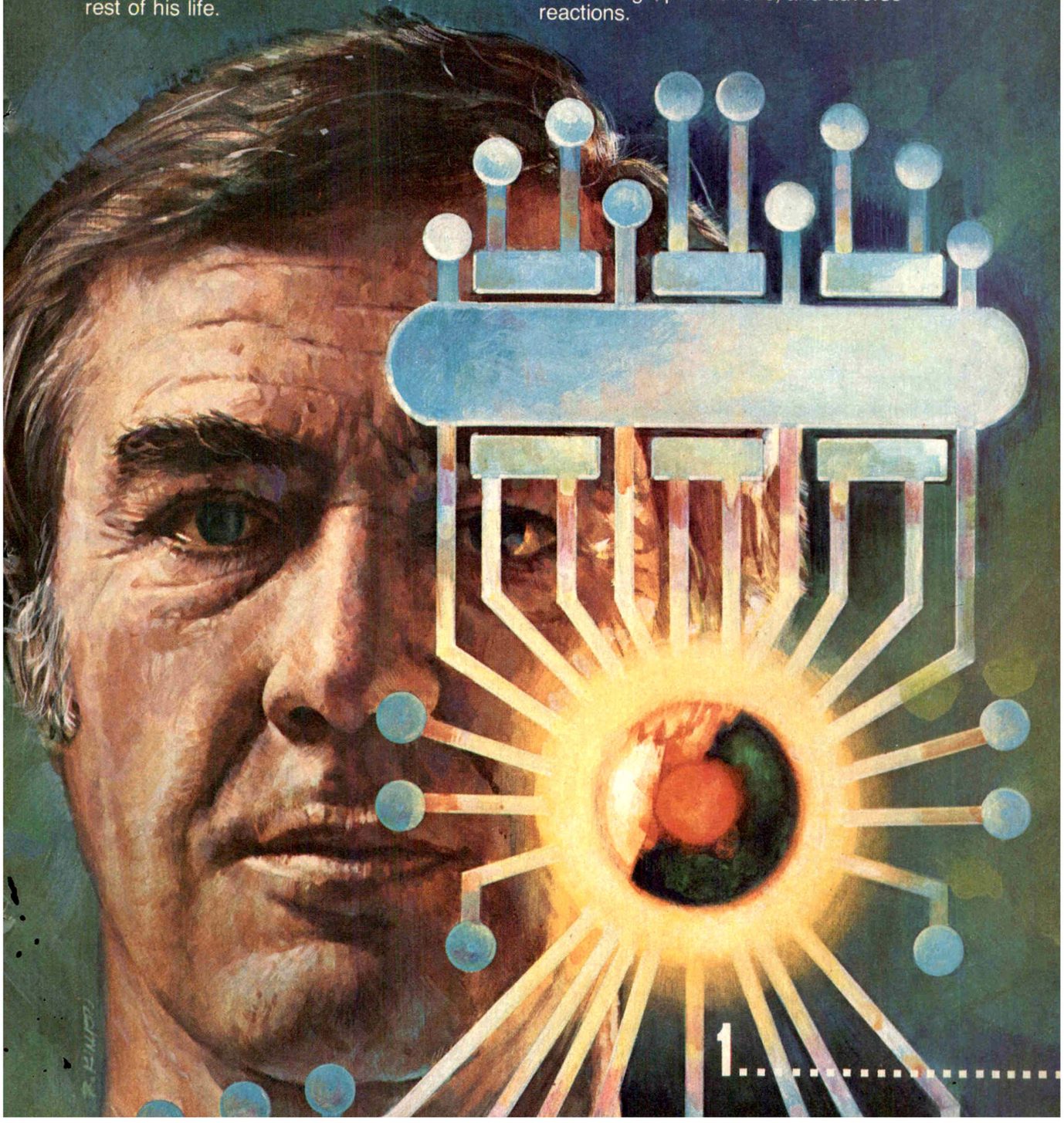
You can improve those odds. Here's how:

1. COUNSEL: Talk to your patient about the disease and its consequences—about strokes, heart attacks, and kidney failure. Tell him he *must* take medication daily, and for the rest of his life.

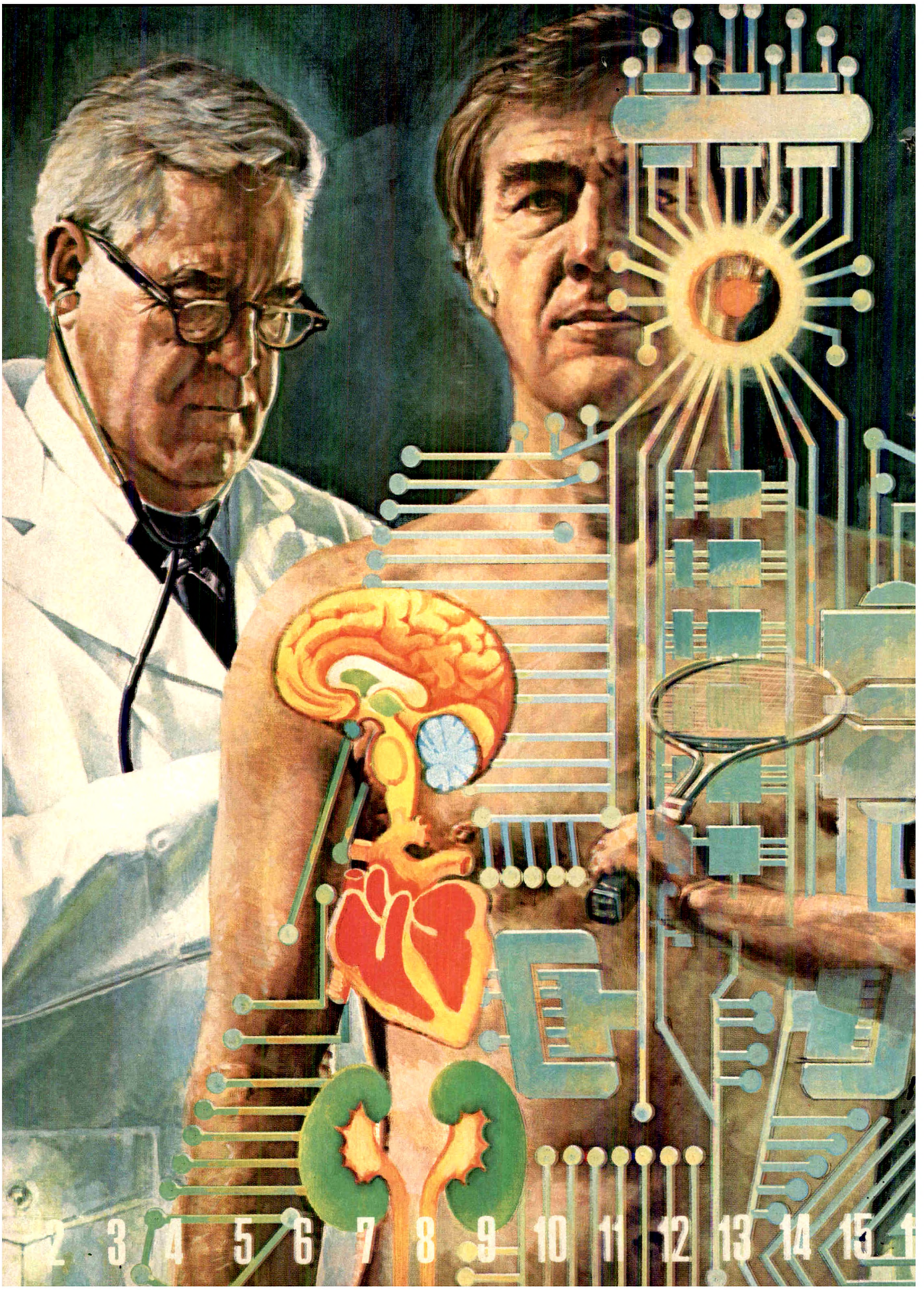
2. CATAPRES® (clonidine hydrochloride): because it works, and people stay with it.[2]

Counsel...and Catapres. They can help change the odds against your patient's future.

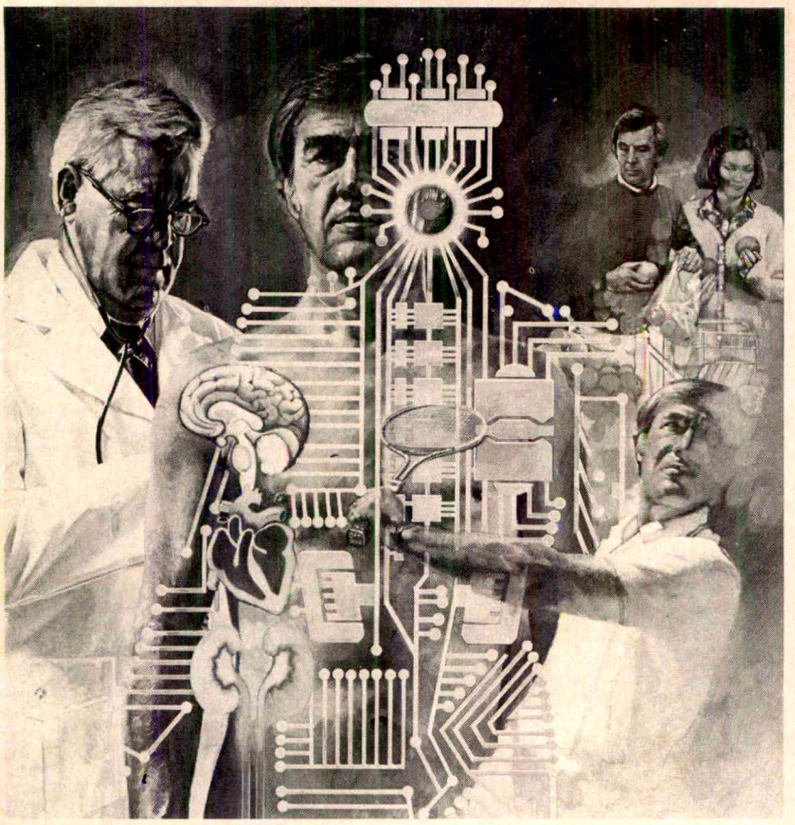
Please see brief summary of prescribing information on last page of this advertisement for warnings, precautions, and adverse reactions.



1.


2 3 4 5 6 7 8 9 10 11 12 13 14 15


Tablets of 0.1 and 0.2 mg
Catapres® (clonidine HCl)
can help you
shape his world
If you've come to expect
only this much of Catapres...
1. smooth lowering of blood pressure
2. effective for all degrees of hypertension (mild to moderate in potency)
3. brain, heart, and kidney blood flow preserved
Ask for more of Catapres
1. no contraindications
2. normal hemodynamics
3. low incidence of depression and orthostatic hypotension
4. no fatal hepatotoxicity
5. excellent record of compliance
Most common side effects are dry mouth, drowsiness and sedation, which generally tend to diminish with time.
Please see brief summary of prescribing information on last page of this advertisement for warnings, precautions, and adverse reactions.
Tablets of 0.1 and 0.2 mg
Catapres® (clonidine HCl)
Hypertension
19 20 21 22 23 24 25 26 27 28 29 30 31



Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl) can help you shape his world

Counsel...and Catapres. They can help change the odds against your patient's future. And to change them even more, ask us for these from your Boehringer representative:

— A major new film "Compliance: State of the Art"[1]
— A compliance monograph
— Patient Aid Booklet
— Patient Worksheets
— Patient Reminder Postcards
— Other effective compliance enhancers

References:
1. Wilber JA, Barrow JS: Am J Med, 52:653-663, 1972.
2. Data on file at Boehringer Ingelheim Ltd.

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Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

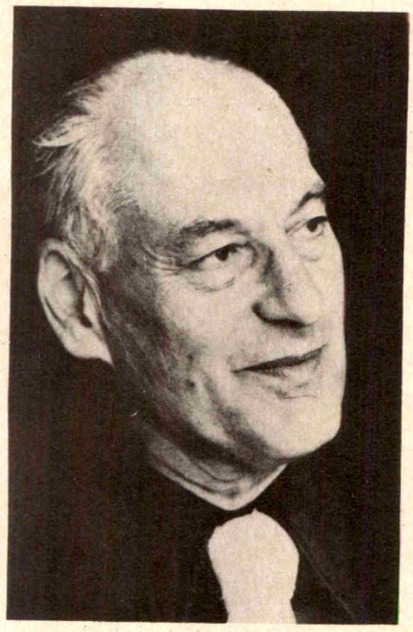
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President's Page

How to Cope With the New Technology? The Knowledge and the Prudence



Borys Surawicz, MD, FACC

Not long ago, Dr. J. W. Hurst included in his textbook the scheme of Dr. W. Proctor Harvey in which the methods of diagnosing heart disease were likened to the five fingers of the hand.[1] In this diagram, the thumb represented the patient's history, the index finger the physical examination, the middle finger the electrocardiogram, the ring finger the chest X-ray film and the little finger all "other diagnostic techniques." The clenched fist symbolized the diagnostic power of the information synthesized from these joint fingers. At that time, the category of "other diagnostic techniques" represented mainly the graphic records of various physical signs and the invasive procedures of cardiac catheterization and angiography. But soon afterwards the emergence of echocardiography upset the balance in the hierarchy of the digits. The addition of the echocardiogram to the little finger carrying "other diagnostic techniques" would most certainly have resulted in the hyperplasia of this finger and a rather unsightly deformity of the diagnostic fist. As a matter of fact, the echocardiogram could justly compete for diagnostic usefulness with the chest X-ray film or the electrocardiogram and seek for itself the status of an independent finger. I suspect that the prospect of polydactyly replacing the fist as a model of the coordinated approach compelled Dr. Hurst to omit the "five finger" diagram from the subsequent edition of the "Heart."[2]

Echocardiography

Echocardiography is still continuing to grow in importance as an extremely useful and versatile tool in research, teaching and the clinical practice of pediatric and adult cardiology. The wholesale acceptance of this technique by cardiologists shows that the benefits of accurate noninvasive technology will be accepted, notwithstanding the psychologic difficulties in adjusting our vision to the restlessness of the curling and twisting zigzags formed by the interfaces of the reflected sound waves, the inconvenience of the long time required to train a competent sonographic technician and the relatively high cost of the new equipment. Today, a cardiovascular trainee is likely to be more familiar with the echocardiographic images of mitral stenosis, prolapsing mitral valve leaflets, pericardial effusion, myxoma, fibrocalcific aortic valve, and many other morphologic and functional abnormalities than with the electrocardiographic and the radiographic patterns of chamber enlargement.

While echocardiography continues to assert itself in more community hospitals and private offices, and the training programs attempt to satisfy the increasing demand for the skilled sonocardiographic technicians, medical technology has not ceased offering us new and more advanced diagnostic tools. We are constantly being asked to test something new even before we have adequately explored the previous novelty, and it is difficult to blame us for our occasional frustrated outcry to the designers and the manufacturers, "And what now?"

Predictably, technology is developing methods for viewing the diagnostic images in more than one dimension, and we have begun appreciating the advantages of a two dimensional motion image over the flat view in one plane. We are not surprised to see that two dimensional echocardiography has already made a very successful debut in the clinical arena, even though different institutions have different models of this very expensive equipment. It must be obvious that the number of possible two dimensional images from a given heart is potentially limitless, because there is no end to the number of plane combinations that we can choose for the synchronized presentations. At the recent 28th Scientific Sessions of the American College of Cardiology in Miami Beach, Florida, two dimensional echocardiography was the principal diagnostic method in about 20 presented papers.[3] While it is still premature to make predictions about the future role of two dimensional echocardiography in cardiac diagnosis, this technique is likely to fare better than the nearly defunct three dimensional movies in our theaters.

Nuclear Imaging

Even the most intensive watchers of the developments in echocardiographic technology cannot ignore the enormous strides made by nuclear cardiology in the past few years. At the recent ACC program in Miami Beach, I found 33 abstracts in which cardiac nuclear imaging was used in a total of 872 patients.[3] It is safe to assume that many thousands of patients in various institutions are being studied in such a manner, yet informal inquiries among individual physicians and groups of practicing cardiologists have convinced me that the role of nuclear techniques is not generally well understood. This applies not only to the methodology but to the diagnostic accuracy, and even to the purposes of these pro-

cedures. Nuclear cardiology still has a reputation of being an investigator's pet, and we are not sure how to connect the newest finger to the mass of the modern fist. In other words, many of us still clamor for a better understanding of why and when we need to look at the nuclear images. In those 33 abstracts of the ACC Scientific Sessions, I have identified the following six main purposes of the clinical nuclear studies in addition to the "hot spot" technetium pyrophosphate scan for the diagnosis of acute infarction:

1. *Assessment of global and regional myocardial perfusion at rest and after exercise.* In this category, most investigators have used thallium-201, but myocardial perfusion has also been studied with radioactive xenon, krypton, labeled ammonia and other positron emission. It seems to me that although thallium-201 is in the forefront, the technological race is not over.

2. *Assessment of left ventricular systolic function, including ejection fraction at rest and after exercise.* For this, some investigators have used multiple gated blood pool scintigrams employing technetium-99 labeled red blood cells or serum albumen. Others have reported equally good or even more accurate results using first pass nuclear angiograms. It seems that the differences in methodology are determined by the availability of the equipment and the experience of the investigator.

3. *Assessment of left ventricular regional wall motion at rest and after exercise.* This also has been studied by means of multigated blood pool scintigrams and first pass nuclear angiograms. Again, it appears that the type of test in a given institution is determined by the available equipment and the experience of the investigator.

4. *Assessment of right ventricular ejection fraction and right ventricular regional wall motion.*

5. *Detection and quantitation of intracardiac shunts.*

6. *Study of myocardial metabolism* utilizing tagged fatty acids or other substrates.

Role of Modern Technology

It is obvious that any nuclear image can be displayed in a variety of computer-generated modes, and it is not surprising that different investigators have their own favorite methods and projections for the display of data. The progress in computer-enhanced imaging and in computerized tomography leads us to a realization that our technology today is capable of providing us with infinitely detailed information about the shape, composition, perfusion, motion and metabolism of even the smallest particle within the heart. Thus, we must consider the role of contemporary technology and be aware that it can inundate us with more information than we can handle in everyday practice. Our problem has become a bit different from one of learning how to synthesize the information by flexing the five familiar fingers into the shape of the good old diagnostic fist. We have come to the point where we no longer want to collect all the available information for the solution to practical problems. We are becoming more concerned with defining what we wish to know about the heart in our patient than with the methodic gathering of the maximal obtainable information. These changes suggest that the new technology has made our lives not easier, but more difficult. We must allot more time to the analysis of the available options, and we must become more selective in the choice of these options. I believe that the former requires more knowledge, and the latter more prudence. In the pursuit of both, we may need to consider new strategies for coping with the overwhelming plethora of information that encroaches on the meager reserves of our spare time. In trying to approach this problem I have sketched out the following sample which represents a step by step strategic approach to deal with the new noninvasive technology in cardiac diagnosis:

Strategy for Coping With the New Technology

1. Acquire some rudimentary understanding of the principles of the technique.
2. Understand the purpose of the technique and the indications for its use.
3. Relate the new technique to the older, familiar techniques in order to learn whether the new technique:
   - A. Reveals some previously unavailable information
   - B. Replaces the older techniques
   - C. Supplements the older techniques
   - D. Merely duplicates the older techniques
4. Understand the limitations of accuracy of the technique.
5. Know the cost of use of the technique.
6. Obtain information about the state of the development of the technique and about the future outlook. Will the procedure be a passing fad, or will it become an established permanent fixture or an intermediate stage in the technologic progress?

State of the Art Conference

I anticipate that many readers will immediately question me about where to look for such a handy package of information about the new noninvasive technology in cardiac diagnosis. I doubt whether a single package of this type is available anywhere, because its production may require an input from more than one person. A state-of-the-art report of such type, including some consensus and reasonable predictions for the future, may require input from a sizable group of experts. I believe that the College could provide a valuable service to its membership by asking these experts to prepare such a document. This could perhaps be accomplished within a framework of a state-of-the-art conference, smaller in scope than our traditional Bethesda Conference but larger than an ordinary task force expressing an expert opinion on a single method or procedure. If the idea of the envisioned state-of-the-art report on the new noninvasive technology in cardiovascular diagnosis will be accepted by the leadership of the College, we will explore with the appropriate committees the feasibility of a concept conference of this type to be set up at Heart House. If successful, such an accomplishment can reward our membership with a concise text summarizing the current and the future status of the new noninvasive technology, and serving as a guide toward prudent utilization of this technology.

Borys Surawicz, MD, FACC
President
American College of Cardiology

References

1. The Heart, Hurst JW, Logue RB, ed, New York, Toronto, Sydney, London, McGraw-Hill 1966, p 44
2. The Heart, Arteries, and Veins (Hurst JW, Logue RB, ed) New York, St Louis, San Francisco, London, Sydney, Toronto, Mexico, Panama, 1970, McGraw-Hill
3. Abstracts of papers presented at the 28th Annual Scientific Session of the American College of Cardiology, Miami Beach, Florida, March 11–15, 1979, Am J Cardiol 43:341–437, 1979

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Robert O. Brandenburg, MD
Minnesota

Task Force on Nomenclature of Arrhythmias

Charles Fisch, MD
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CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

JUNE 1979 THROUGH NOVEMBER 1979

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

To be arranged individually — **Preceptorships in Echocardiography.** Joel Morganroth, FACC, director. Lankenau Hospital, Philadelphia, PA

To be arranged individually — **Preceptorships in Cardiology.** Jules Constant, FACC, director. Buffalo General Hospital, Buffalo, NY

JUNE 8–10 — **Cardiac Auscultation Workshops.** Jules Constant, FACC, director. Niagara Hilton Hotel, Niagara Falls, NY

JUNE 13–16 — **Sixth Annual Symposium. Clinical Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** Arthur D. Hagan, FACC, director and William F. Friedman, FACC and Walter V. R. Vieweg, FACC, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

JUNE 21–23 — **Medical and Surgical Management of Coronary Artery Disease.** M. Leo Hughes, Jr., FACC, director and Robert C. K. Riggins and Richard P. Anderson, co-directors. Virginia Mason Medical Center, Seattle, WA

AUG. 25–27 — **Tutorials in the Tetons: Cardiac Emergencies (Fifth Annual).** Robert S. Eliot, FACC and Alan D. Forker, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Moran, WY

SEPT. 10–13 — **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC, director and Charles Fisch, FACC, co-director. Wishard Memorial Hospital, Indiana University Medical Center, Indianapolis, IN

SEPT. 10–13 — **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Fairmont Hotel, San Francisco, CA

SEPT. 17–19 — **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya, James C. Dillon, FACC and Arthur E. Weyman, FACC, codirectors. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 11–13 — **New Concepts in the Management of Congestive Heart Failure.** Peter C. Gazes, FACC, director and Charles P. Summerall, III, FACC, Grady H. Hendrix, FACC, William H. Barnwell, II, FACC, Bruce W. Usher, FACC, J. Lindsay Leviner, FACC, Robert G. Irvin, FACC and Larry E. Kibler, co-directors. Kiawah Island Inn, Kiawah Island, Charleston, SC

OCT. 18–20 — **Cardiology Update—1979.** William W. Parmley, FACC and Kanu Chatterjee, FACC, co-directors. Del Monte Hyatt House, Monterey, CA

OCT. 22–23 — **Correlations in Ischemic Heart Disease.** Leonard S. Gettes, FACC, director. Carolina Inn, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC

OCT. 25–27 — **New Techniques and Concepts in Cardiology. Coronary Artery Disease: Rehabilitation, Surgery, Coronary Spasm, Balloon Dilatation; Valvular Heart Disease; Hypertrophic Cardiomyopathy.** Stephen E. Epstein, FACC, director. Hyatt Regency Hotel, Washington, DC

NOV. 5–14 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, co-directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda Maryland headquarters, began operations in October 1977 with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1979, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

JUNE 1979 THROUGH NOVEMBER 1979

Month/Dates	Course Director	Title of Program
June 11–13	Shahbudin H. Rahimtoola, MD, FACC	**Valvular Heart Disease**
June 20–22	Michael S. Gordon, MD, FACC	**Cardiac Auscultation**
June 25–27	Sylvan L. Weinberg, MD, FACC	**CCU Update for Nursing Supervisors**
July 5–7	G. Charles Oliver, MD, FACC	**Ambulatory Monitoring and Sudden Death**
Sept. 5–7	J. O'Neal Humphries, MD	**Coronary Care Units: 15 Years Later**
Sept. 10–12	Dan G. McNamara, MD	**Pediatric Cardiology**
Sept. 17–19	Louis Lemberg, MD	**CCU Update for Nursing Supervisors**
Sept. 24–26	Kenneth M. Rosen, MD	**Evaluation of Arrhythmias With His Bundle Recording and Stimulation**
Sept. 27–28	Douglas P. Zipes, MD	**The New Generation Pacemaker**
Oct. 8–10	Leonard S. Dreifus, MD	**Interpretation and Therapy of Cardiac Arrhythmias**
Oct. 15–17	Marvin Moser, MD	**Hypertension**
Oct. 29–31	Max Harry Weil, MD	**Emergency Care of the Critically Ill Patient**
Nov. 1–3	Barrie Levitt, MD	**Cardiovascular Pharmacology**
Nov. 28–30	William W. Parmley, MD	**Non-invasive Cardiovascular Procedure: Sensitivity and Specificity**

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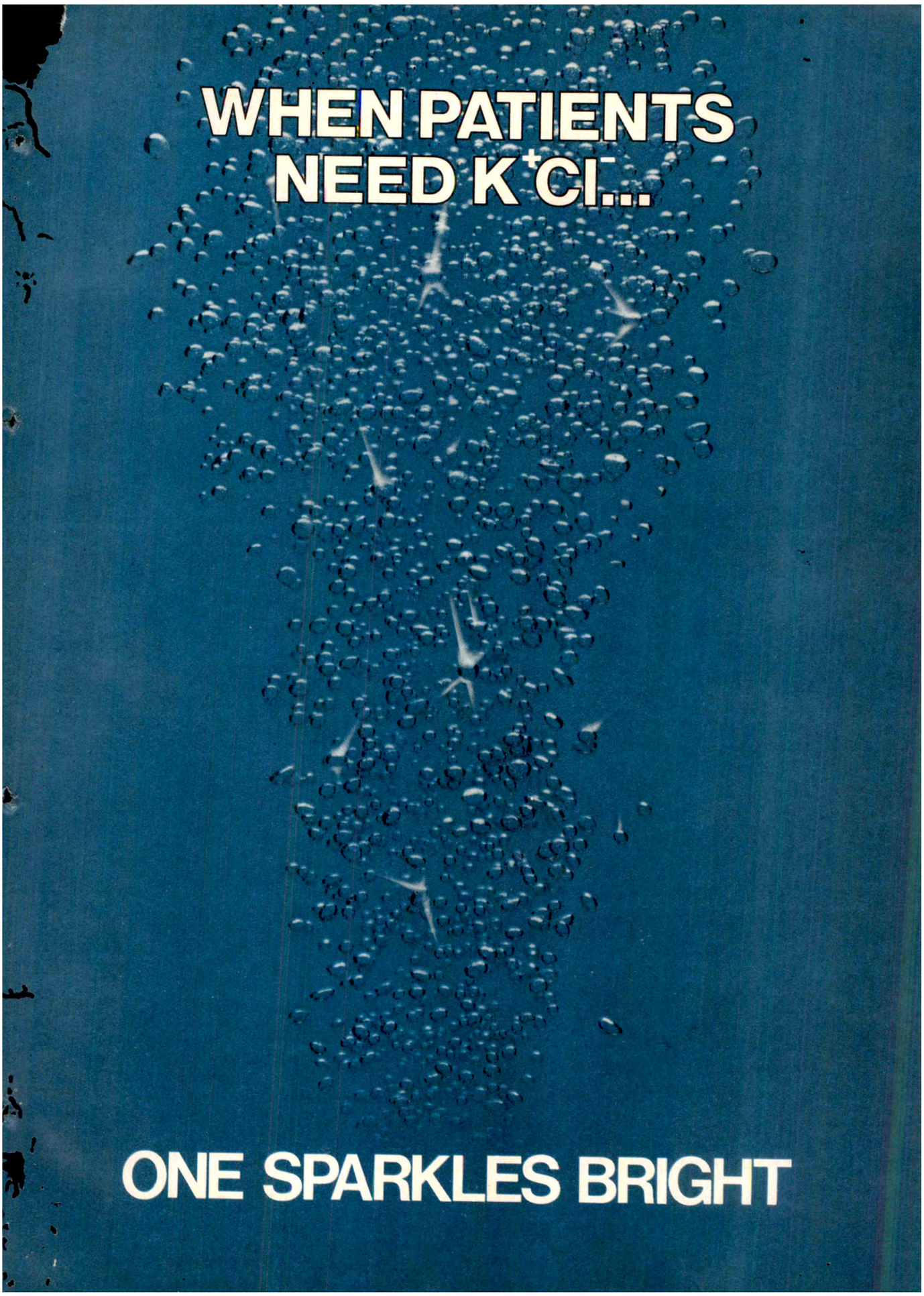
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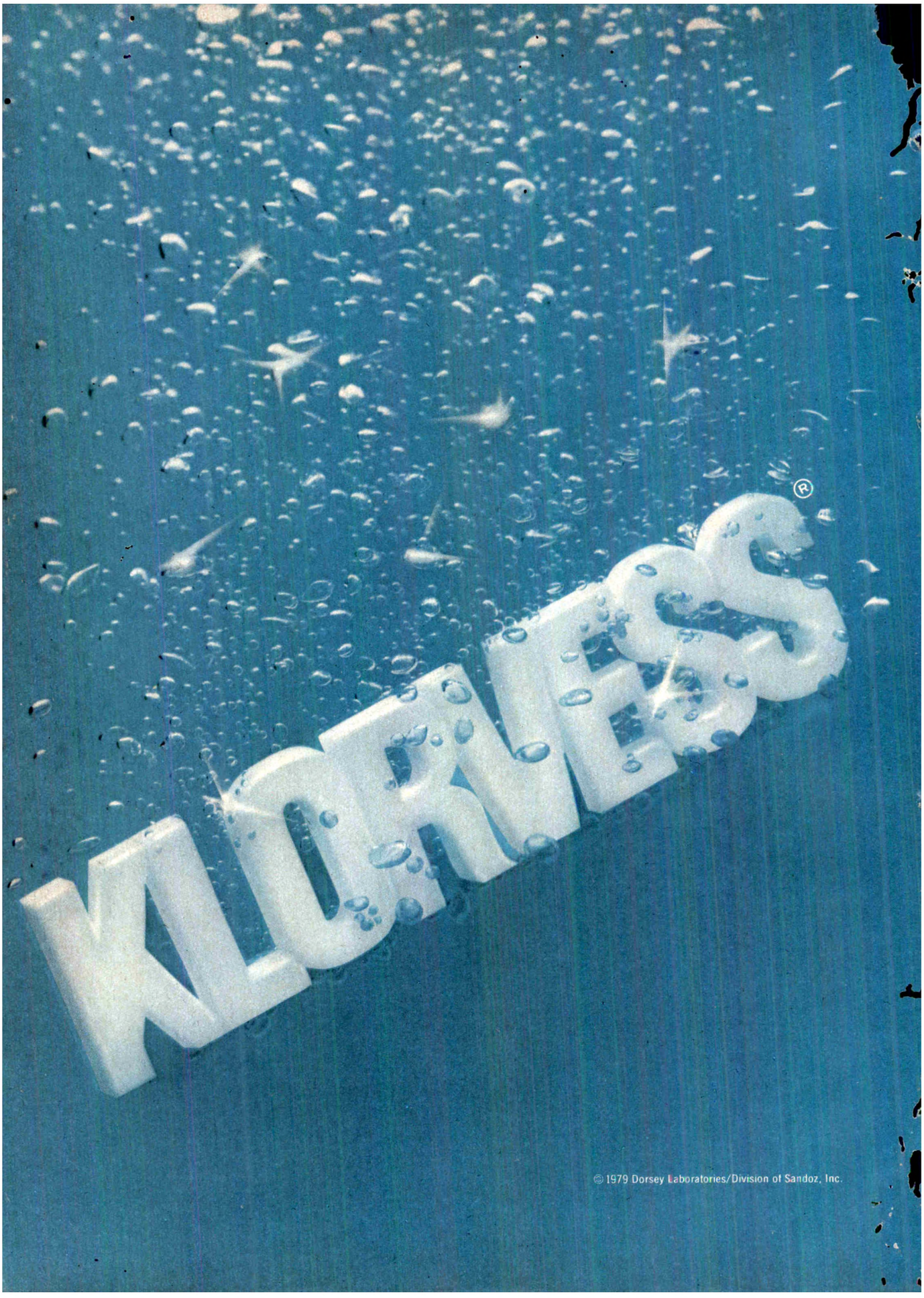
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Please see brief summary of prescribing information on adjoining page.

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Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

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For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

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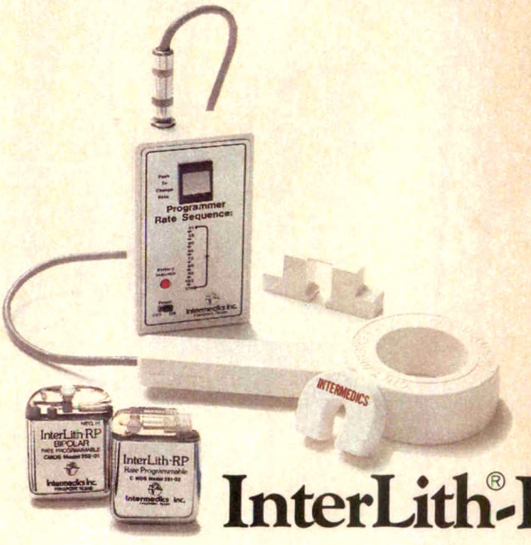
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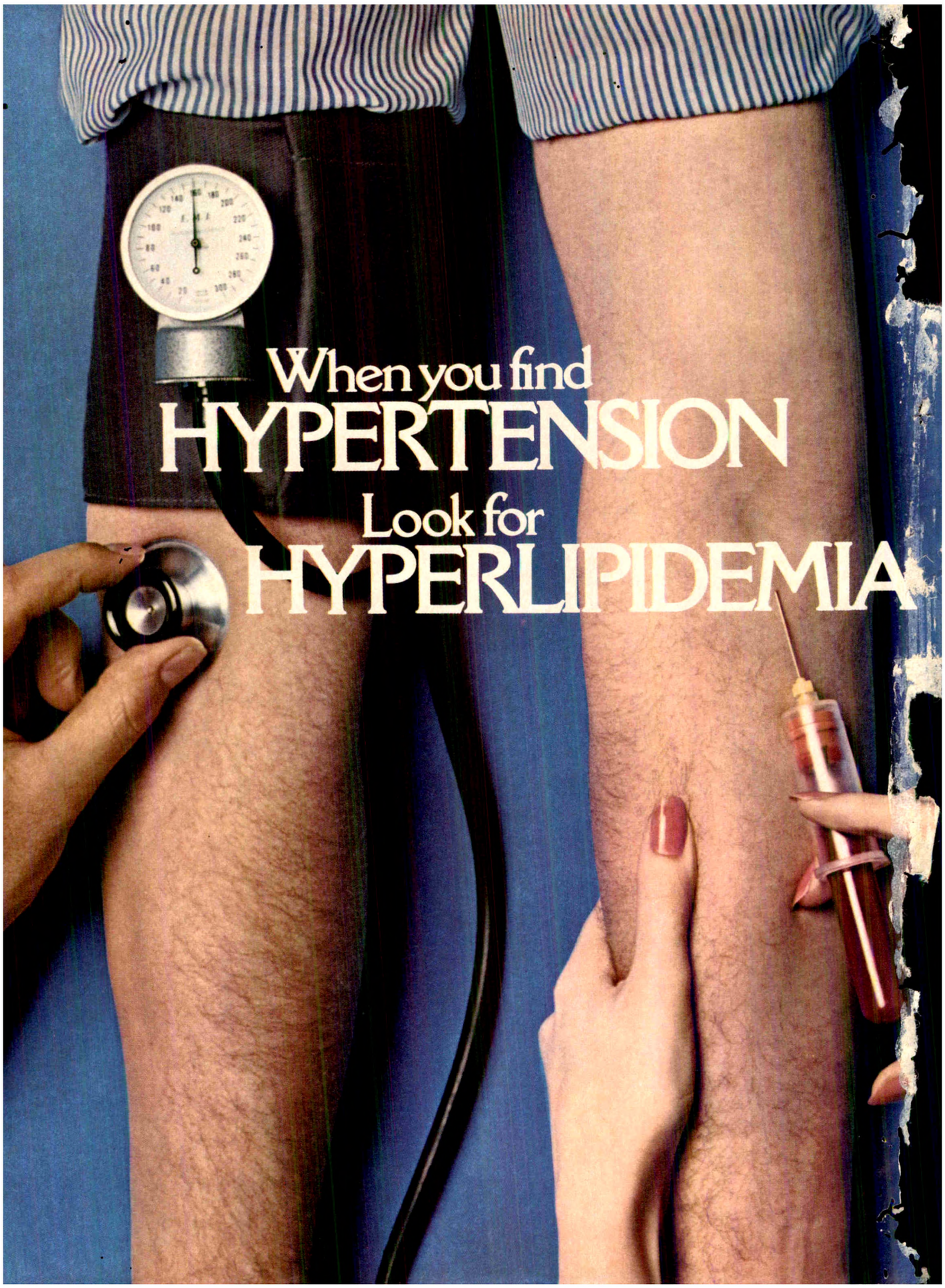
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When you find
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Two out of every five hypertensives found to be hyperlipidemic in recent study[1]

Lipid abnormalities are often part of a broader clinical picture. For example, a recent study[1] reports an association between hypertension and hypertriglyceridemia—the most common form of hyperlipidemia. (See table below.)

Type of Hyperlipidemia*	Incidence of Hyperlipidemia	
	Hypertensives (89 subjects)	Normotensives (89 subjects)
Type IIA	9% (8)	7% (6)
Type IIB	6% (5)	3% (3)
Type IV	26% (23)	11% (10)
Total	**41% (36)**	**21% (19)**

*Hyperlipidemia was diagnosed when cholesterol levels exceeded 282 mg% and/or triglycerides were over 177 mg%—cutoff points higher than the usual upper limits of normal.
Adapted from Thomas, G. W., *et al.*[1]

The essential measurements—cholesterol *and* triglycerides

Today, lipid determinations are recommended as part of every general medical examination.

Because elevated lipids may coexist with high blood pressure, it is especially important to screen hypertensive patients for hyperlipidemia. Testing for both cholesterol *and* triglycerides is considered essential,[2-5] since it increases the chances of detection from 6 out of 10 to 9.5 out of 10.[6]

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

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In clinical studies involving patients with drug-responsive hyperlipoproteinemia, diet plus ATROMID-S (clofibrate) lowered serum cholesterol levels from 22% to as much as 52% and reduced triglyceride values over a range of 19% to 80%.[7-12]

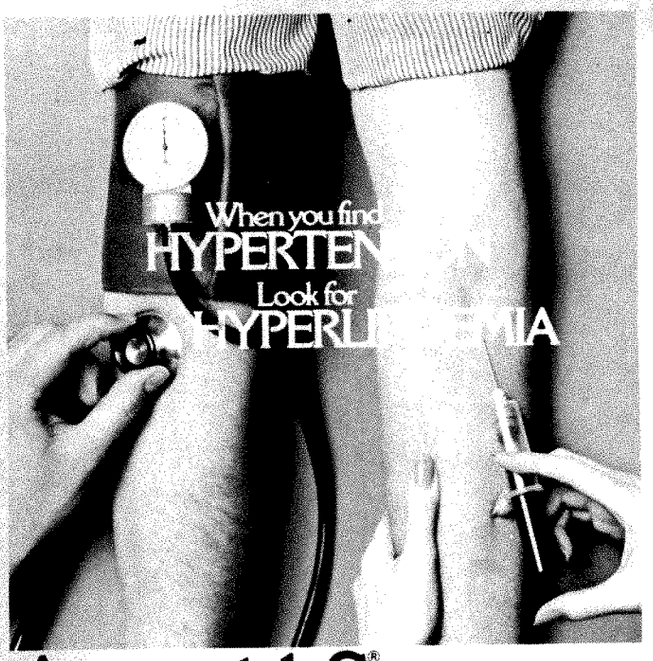
Patient acceptance is generally good

In more than a decade of use, clofibrate has been generally well tolerated. Major adverse effects are primarily gastrointestinal, with nausea being predominant. Other G.I. reactions include loose stools, flatulence, abdominal distress, and, infrequently, gallstones. Less common reactions include muscle cramping, myalgia, and alopecia. Please see "Important Note" at left and Warning on concomitant anticoagulant usage in prescribing information on following page.

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BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® Brand of clofibrate

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy in patients who do not respond adequately to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

Administration of clofibrate to mice and rats in long-term studies at eight times the human dose resulted in a higher incidence of liver tumors than in controls. Lower doses were not studied. Although the relevance of this finding to humans is not known at this time, it cannot be dismissed especially since this drug is intended for long-term administration. ATROMID-S should be used only in patients with hyperlipidemia who do not respond adequately to dietary intervention.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long-term administration of a drug of this nature, adequate baseline studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original baseline may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT, SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial*: The recommended dosage for adults is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate. In bottles of 100.

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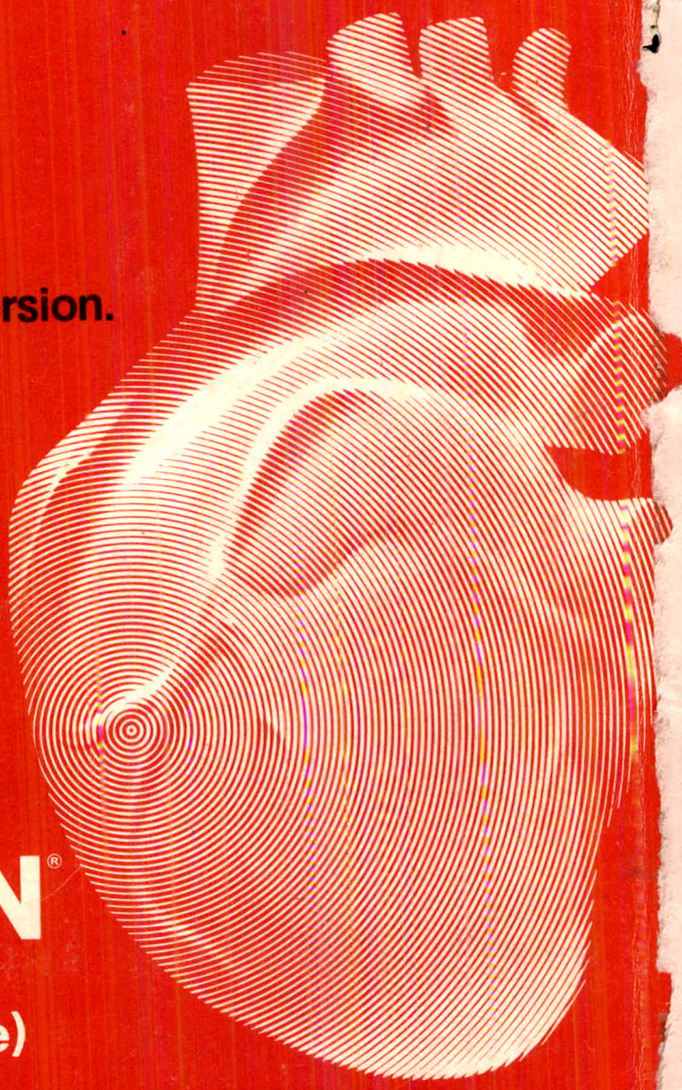
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*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICAT ONS: CARDIOQUIN Tablets (quinidi polygalacturonate) are indicated in the treatment of: premature atr and ventricular contractions; paroxysmal atrial tachycardia; paroxy mal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillati established atrial fibrillation when therapy is appropriate; paroxysm ventricular tachycardia wher not associated with complete ha block; maintenance therapy after electrical conversion of atrial fib lation and/or flutter. CONTRAINDICATIONS: Aberrant impulses a abnormal rhythms due to escape mechanisms should not be tre with quinidine. WARNING: In the treatment of atrial flutter revers to sinus rhythm may be preceded by a progressive reduction in degree of AV block to a 1:1 ratio and resulting extremely rapid v tricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinid polygalacturonate 275 mg.) is equivalent in quinidine content t grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosa must be adjusted to individual needs, both for conversion and ma tenance. An initial dose of 1 to 3 tablets may be used to termin arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhyth is not restored after 3 or 4 equal doses, the dose may be increas by ½ to 1 tablet (137.5 to 275 mg.) and administered three to fo times before any further dosage increase. For maintenance, o tablet may be used two to three times a day; generally one tab morning and night will be adequate. SUPPLIED: Uncoated, scor tablets in bottles of 100.

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